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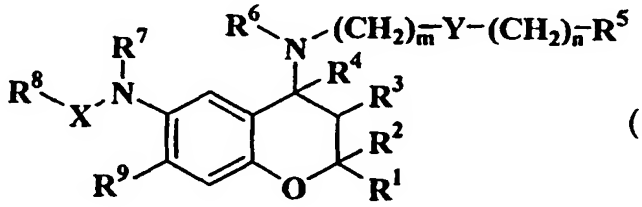
(54) Title: BENZOPYRAN DERIVATIVE



(I)

(57) Abstract: This invention relates a benzopyran derivative of formula (I) wherein, R^1 and R^2 represent each independently a hydrogen atom, a (substituted)C_{1-6} alkyl group or a (substituted)phenyl group,R^3 represents a hydroxyl group or C_{1-6} alkylcarbonyloxy group, R^4 represents a hydrogen atom, or R^3 and R^4 together form a bond, m represents an integer of 0-4, n represents an integer of 0-4, Y is absent, or represents $CR^{11}R^{12}$ in which R^{11} and R^{12} represent each independently a hydrogen atom or a C_{1-6} alkyl group, R^5 represents an aryl group or a (substituted)heteroaryl group,R^6 represents a hydrogen atom or a C_{1-6} alkyl group,R^7 represents a hydrogen atom or a C_{1-6} alkyl group,X is absent, or represents C=O or SO_2, R^8 represents a hydrogen atom, a (substituted)C_{1-6} alkyl group or C^{3-6} cycloalkyl group, and R^9 represents a nitro group, etc., or a pharmaceutically acceptable salt thereof. And this invention also relates an antiarrhythmic agent having the prolongation effect on the functional refractory period comprising said compound or a pharmaceutically acceptable salt thereof as an active ingredient.

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DESCRIPTION

BENZOPYRAN DERIVATIVE

Technical Field

The present invention relates to benzopyran derivatives having a prolongation effect on the functional refractory period, which are used for treatments of arrhythmia in mammal including human beings.

Background Art

As benzopyran derivatives, there have been known 4-acylaminobenzopyran derivatives exemplified by Cromakalim (Japanese Patent Application Laid-Open No. Sho 58-67683). These 4-acylaminobenzopyran derivatives exemplified by Cromakalim are known to open an ATP sensitive K^+ channel and to be effective for the treatment of hypertension or asthma, but there has not been any mention as to the treatment for arrhythmia based on the prolongation effect on the functional refractory period.

Now, conventional antiarrhythmic agents having the prolongation effect on the functional refractory period as a main function (such as Class I drugs of antiarrhythmic agent classification according to Vaughan Williams, or d-sotalol belonging to Class III) have highly dangerous arrhythmic inducing actions that can result in sudden death such as torsades de pointes based on extension of ventricular muscle action potential relating to the prolongation effect on the functional refractory period, which become the therapeutic problems. Thus, agents having less side effects are desired.

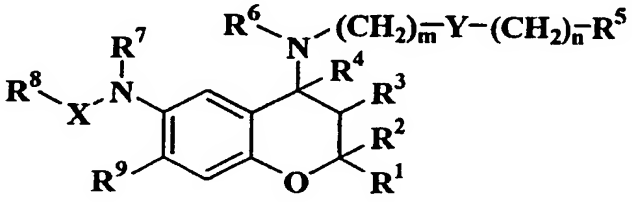
Disclosure of Invention

The inventors of the present invention have made an intensive study of compounds having the prolongation effect on the functional refractory period more selective for atrium muscle than for ventricular muscle, and found that the compound of the general formula (I) has a prolongation effect on the functional refractory

period selective for atrium muscle without any influence on the refractory period of ventricular muscle and action potential parameters.

The inventors of the present invention have studied eagerly benzopyran derivatives, and found that the compound of the formula (I) has the strong prolongation effect on the functional refractory period, and it is useful as an antiarrhythmic agent. The present invention has been made based on this finding.

The present invention relates to a benzopyran derivative of the formula (I)



(I)

wherein, R^1 and R^2 represent each independently a hydrogen atom, a C_{1-6} alkyl group in which the alkyl group may be optionally substituted with a halogen atom, a C_{1-6} alkoxy group or a hydroxyl group; or a phenyl group in which the phenyl group may be optionally substituted with a halogen atom, a hydroxyl group, a nitro group, a cyano group, a C_{1-6} alkyl group or a C_{1-6} alkoxy group,

R^3 represents a hydroxyl group or C_{1-6} alkylcarbonyloxy group,

R^4 represents a hydrogen atom, or R^3 and R^4 together form a bond,

m represents an integer of 0-4,

n represents an integer of 0-4,

Y is absent, or represents $CR^{11}R^{12}$, in which R^{11} and R^{12} represent each independently a hydrogen atom or a C_{1-6} alkyl group,

R^5 represents an aryl group or a heteroaryl group in which the aryl group and the heteroaryl group may be optionally substituted with $q\cdot(R^{10})$, in which R^{10} represents a halogen atom, a hydroxyl group, a C_{1-6} alkyl group in which the alkyl group may be optionally substituted with a halogen atom or a C_{1-6} alkoxy group; or R^{10} represents a nitro group, a cyano group, a formyl group, a

formamide group, an amino group, a C_{1-6} alkylamino group, a di-C_{1-6}alkylamino group, a C_{1-6} alkylcarbonylamino group, a C_{1-6} alkylsulfonylamino group, an aminocarbonyl group, a C_{1-6} alkylaminocarbonyl group, a di-C_{1-6} alkylaminocarbonyl group, a C_{1-6} alkylcarbonyl group, a C_{1-6} alkoxycarbonyl group, an aminosulfonyl group, a C_{1-6} alkylsulfonyl group, a carboxyl group or an arylcarbonyl group, q represents an integer of 1-3, and each R^{10} may be same or different if q represents 2 or 3,

R^6 represents a hydrogen atom or a C_{1-6} alkyl group,

R^7 represents a hydrogen atom or a C_{1-6} alkyl group,

X is absent, or represents C=O or SO_2,

R^8 represents a hydrogen atom, a C_{1-6} alkyl group in which the alkyl group may be optionally substituted with a halogen atom, a hydroxyl group or a C_{1-6} alkoxy group; or C_{3-6} cycloalkyl group, and

R^9 represents a hydrogen atom, a halogen atom, a nitro group or a cyano group;

or a pharmaceutically acceptable salt thereof.

The compound according to the present invention has the strong prolongation effect on the functional refractory period and it can be used as a drug for treating arrhythmia.

Respective substituents for the compound (I) according to the present invention are illustrated specifically as follows.

Herein, "n" means normal, "i" means iso, "s" means secondary, "t" means tertiary, "c" means cyclo, "o" means ortho, "m" means meta, and "p" means para.

As C_{1-6} alkyl groups, there may be mentioned methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, 1-pentyl, 2-pentyl, 3-pentyl, i-pentyl, neopentyl, 2,2-dimethylpropyl, 1-hexyl, 2-hexyl, 3-hexyl, 1-methyl-n-pentyl, 1,1,2-trimethyl-n-propyl, 1,2,2-trimethyl-n-propyl, 3,3-dimethyl-n-butyl, trifluoromethyl, trifluoroethyl, pentafluoroethyl, cyanomethyl and hydroxymethyl, etc.

Preferably, there may be mentioned methyl, ethyl, n-propyl, i-propyl and n-butyl.

As halogen atoms, there may be mentioned a fluorine atom, a chlorine atom, a bromine atom and an iodine atom. Preferably, there

may be mentioned a fluorine atom, a chlorine atom and a bromine atom.

As C_{1-6} alkoxy groups, there may be mentioned methoxy, trifluoromethoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, s-butoxy, t-butoxy, 1-pentyloxy, 2-pentyloxy, 3-pentyloxy, i-pentyloxy, neopentyloxy, 2,2-dimethylpropoxy, 1-hexyloxy, 2-hexyloxy, 3-hexyloxy, 1-methyl-n-pentyloxy, 1,1,2-trimethyl-n-propoxy, 1,2,2-trimethyl-n-propoxy and 3,3-dimethyl-n-butoxy, etc.

Preferably, there may be mentioned methoxy, ethoxy, n-propoxy and i-propoxy.

As C_{1-6} alkylcarbonyloxy groups, there may be mentioned methylcarbonyloxy, ethylcarbonyloxy, n-propylcarbonyloxy, i-propylcarbonyloxy, n-butylcarbonyloxy, i-butylcarbonyloxy, s-butylcarbonyloxy, t-butylcarbonyloxy, 1-pentylcarbonyloxy, 2-pentylcarbonyloxy, 3-pentylcarbonyloxy, i-pentylcarbonyloxy, neopentylcarbonyloxy, t-pentylcarbonyloxy, 1-hexylcarbonyloxy, 2-hexylcarbonyloxy, 3-hexylcarbonyloxy, 1-methyl-n-pentylcarbonyloxy, 1,1,2-trimethyl-n-propylcarbonyloxy, 1,2,2-trimethyl-n-propylcarbonyloxy and 3,3-dimethyl-n-butylcarbonyloxy, etc.

Preferably, there may be mentioned methylcarbonyloxy, ethylcarbonyloxy, n-propylcarbonyloxy, i-propylcarbonyloxy, n-butylcarbonyloxy and t-butylcarbonyloxy.

As aryl groups, there may be mentioned phenyl, biphenyl, naphthyl, anthryl and phenanthryl, etc.

Preferably, there may be mentioned phenyl, biphenyl and naphthyl.

As heteroaryl groups, there may be mentioned 2-thienyl, 3-thienyl, 2-furyl, 3-furyl, 2-pyranyl, 3-pyranyl, 4-pyranyl, 2-benzofuranyl, 3-benzofuranyl, 4-benzofuranyl, 5-benzofuranyl, 6-benzofuranyl, 7-benzofuranyl, 1-isobenzofuranyl, 4-isobenzofuranyl, 5-isobenzofuranyl, 2-benzothienyl, 3-benzothienyl, 4-benzothienyl, 5-benzothienyl, 6-benzothienyl, 7-benzothienyl, 1-isobenzothienyl, 4-isobenzothienyl, 5-isobenzothienyl, 2-chromenyl, 3-chromenyl, 4-chromenyl, 5-

chromenyl, 6-chromenyl, 7-chromenyl, 8-chromenyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 1-imidazolyl, 2-imidazolyl, 4-imidazolyl, 1-pyrazolyl, 3-pyrazolyl, 4-pyrazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 3-isothiazolyl, 4-isothiazolyl, 5-isothiazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrazinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 3-pyridazinyl, 4-pyridazinyl, 1-indolizinyl, 2-indolizinyl, 3-indolizinyl, 5-indolizinyl, 6-indolizinyl, 7-indolizinyl, 8-indolizinyl, 1-isoindolyl, 4-isoindolyl, 5-isoindolyl, 1-indolyl, 2-indolyl, 3-indolyl, 4-indolyl, 5-indolyl, 6-indolyl, 7-indolyl, 1-indazolyl, 2-indazolyl, 3-indazolyl, 4-indazolyl, 5-indazolyl, 6-indazolyl, 7-indazolyl, 1-purinyl, 2-purinyl, 3-purinyl, 6-purinyl, 7-purinyl, 8-purinyl, 2-quinolyl, 3-quinolyl, 4-quinolyl, 5-quinolyl, 6-quinolyl, 7-quinolyl, 8-quinolyl, 1-isoquinolyl, 3-isoquinolyl, 4-isoquinolyl, 5-isoquinolyl, 6-isoquinolyl, 7-isoquinolyl, 8-isoquinolyl, 1-phthalazinyl, 5-phthalazinyl, 6-phthalazinyl, 2-naphthyridinyl, 3-naphthyridinyl, 4-naphthyridinyl, 2-quinoxalinyl, 5-quinoxalinyl, 6-quinoxalinyl, 2-quinazolinyl, 4-quinazolinyl, 5-quinazolinyl, 6-quinazolinyl, 7-quinazolinyl, 8-quinazolinyl, 3-cinnolinyl, 4-cinnolinyl, 5-cinnolinyl, 6-cinnolinyl, 7-cinnolinyl, 8-cinnolinyl, 2-pteridinyl, 4-pteridinyl, 6-pteridinyl, 7-pteridinyl and 3-furazanyl, etc.

Preferably, there may be mentioned 2-pyridyl , 3-pyridyl and 4-pyridyl, etc.

As C_{1-6} alkylamino groups, there may be mentioned methylamino, ethylamino, n-propylamino, i-propylamino, c-propylamino, n-butylamino, i-butylamino, s-butylamino, t-butylamino, c-butylamino, 1-pentylamino, 2-pentylamino, 3-pentylamino, i-pentylamino, neopentylamino, t-pentylamino, c-pentylamino, 1-hexylamino, 2-hexylamino, 3-hexylamino, c-hexylamino, 1-methyl-n-pentylamino, 1,1,2-trimethyl-n-propylamino, 1,2,2-trimethyl-n-propylamino and 3,3-dimethyl-n-butylamino, etc.

Preferably, there may be mentioned methylamino, ethylamino, n-propylamino, i-propylamino and n-butylamino.

As di-C_{1-6} alkylamino groups, there may be mentioned dimethylamino, diethylamino, di-n-propylamino, di-i-propylamino, di-c-propylamino, di-n-butylamino, di-i-butylamino, di-s-butylamino, di-t-butylamino, di-c-butylamino, di-1-pentylamino, di-2-pentylamino, di-3-pentylamino, di-i-pentylamino, di-neopentylamino, di-t-pentylamino, di-c-pentylamino, di-1-hexylamino, di-2-hexylamino, di-3-hexylamino, di-c-hexylamino, di-(1-methyl-n-pentyl)amino, di-(1,1,2-trimethyl-n-propyl)amino, di-(1,2,2-trimethyl-n-propyl)amino, di-(3,3-dimethyl-n-butyl)amino, methyl(ethyl)amino, methyl(n-propyl)amino, methyl(i-propyl)amino, methyl(c-propyl)amino, methyl(n-butyl)amino, methyl(i-butyl)amino, methyl(s-butyl)amino, methyl(t-butyl)amino, methyl(c-butyl)amino, ethyl(n-propyl)amino, ethyl(i-propyl)amino, ethyl(c-propyl)amino, ethyl(n-butyl)amino, ethyl(i-butyl)amino, ethyl(s-butyl)amino, ethyl(t-butyl)amino, ethyl(c-butyl)amino, n-propyl(i-propyl)amino, n-propyl(c-propyl)amino, n-propyl(n-butyl)amino, n-propyl(i-butyl)amino, n-propyl(s-butyl)amino, n-propyl(t-butyl)amino, n-propyl(c-butyl)amino, i-propyl(c-propyl)amino, i-propyl(n-butyl)amino, i-propyl(i-butyl)amino, i-propyl(s-butyl)amino, i-propyl(t-butyl)amino, i-propyl(c-butyl)amino, c-propyl(n-butyl)amino, c-propyl(i-butyl)amino, c-propyl(s-butyl)amino, c-propyl(t-butyl)amino, c-propyl(c-butyl)amino, n-butyl(i-butyl)amino, n-butyl(s-butyl)amino, n-butyl(t-butyl)amino, n-butyl(c-butyl)amino, i-butyl(s-butyl)amino, i-butyl(t-butyl)amino, i-butyl(c-butyl)amino, s-butyl(t-butyl)amino, s-butyl(c-butyl)amino and t-butyl(c-butyl)amino, etc.

Preferably, there may be mentioned dimethylamino, diethylamino, di-n-propylamino, di-i-propylamino and di-n-butylamino.

As C_{1-6} alkylcarbonylamino groups, there may be mentioned methylcarbonylamino, ethylcarbonylamino, n-propylcarbonylamino, i-propylcarbonylamino, n-butylcarbonylamino, i-butylcarbonylamino, s-butylcarbonylamino, t-butylcarbonylamino, 1-pentylcarbonylamino, 2-pentylcarbonylamino, 3-penylcarbonylamino, i-pentylcarbonylamino, neopentylcarbonylamino, t-pentyl-

carbonylamino, 1-hexylcarbonylamino, 2-hexylcarbonylamino and 3-hexylcarbonylamino, etc.

Preferably, there may be mentioned methylcarbonylamino, ethylcarbonylamino, n-propylcarbonylamino, i-propylcarbonylamino and n-butylcarbonylamino.

As C_{1-6} alkylsulfonylamino groups, there may be mentioned methylsulfonylamino, ethylsulfonylamino, n-propylsulfonylamino, i-propylsulfonylamino, n-butylsulfonylamino, i-butylsulfonylamino, s-butylsulfonylamino, t-butylsulfonylamino, 1-pentylsulfonylamino, 2-pentylsulfonylamino, 3-pentylsulfonylamino, i-pentylsulfonylamino, neopentylsulfonylamino, t-pentylsulfonylamino, 1-hexylsulfonylamino, 2-hexylsulfonylamino and 3-hexylsulfonylamino, etc.

Preferably, there may be mentioned methylsulfonylamino, ethylsulfonylamino, n-propylsulfonylamino, i-propylsulfonylamino and n-butylsulfonylamino.

As C_{1-6} alkylaminocarbonyl groups, there may be mentioned methylaminocarbonyl, ethylaminocarbonyl, n-propylaminocarbonyl, i-propylaminocarbonyl, n-butylaminocarbonyl, i-butylaminocarbonyl, s-butylaminocarbonyl, t-butylaminocarbonyl, 1-pentylaminocarbonyl, 2-pentylaminocarbonyl, 3-pentylaminocarbonyl, i-pentylaminocarbonyl, neopentylaminocarbonyl, t-pentylaminocarbonyl, 1-hexylaminocarbonyl, 2-hexylaminocarbonyl and 3-hexylaminocarbonyl, etc.

Preferably, there may be mentioned methylaminocarbonyl, ethylaminocarbonyl, n-propylaminocarbonyl, i-propylaminocarbonyl and n-butylaminocarbonyl.

As di-C_{1-6} alkylaminocarbonyl groups, there may be mentioned dimethylaminocarbonyl, diethylaminocarbonyl, di-n-propylaminocarbonyl, di-i-propylaminocarbonyl, di-c-propylaminocarbonyl, di-n-butylaminocarbonyl, di-i-butylaminocarbonyl, di-s-butylaminocarbonyl, di-t-butylaminocarbonyl, di-c-butylaminocarbonyl, di-1-pentylaminocarbonyl, di-2-pentylaminocarbonyl, di-3-pentylaminocarbonyl, di-i-pentylaminocarbonyl, di-neopentylaminocarbonyl, di-t-pentylaminocarbonyl, di-c-pentylaminocarbonyl, di-1-hexylaminocarbonyl, di-2-hexyl-

aminocarbonyl and di-3-hexylaminocarbonyl, etc.

Preferably, there may be mentioned dimethylaminocarbonyl, diethylaminocarbonyl, di-n-propylaminocarbonyl, di-i-propylaminocarbonyl, di-c-propylaminocarbonyl and di-n-butylaminocarbonyl.

As C_{1-6} alkylcarbonyl groups, there may be mentioned methylcarbonyl, ethylcarbonyl, n-propylcarbonyl, i-propylcarbonyl, n-butylcarbonyl, i-butylcarbonyl, s-butylcarbonyl, t-butylcarbonyl, 1-pentylcarbonyl, 2-pentylcarbonyl, 3-pentylcarbonyl, i-pentylcarbonyl, neopentylcarbonyl, t-pentylcarbonyl, 1-hexylcarbonyl, 2-hexylcarbonyl and 3-hexylcarbonyl.

Preferably, there may be mentioned methylcarbonyl, ethylcarbonyl, n-propylcarbonyl, i-propylcarbonyl and n-butylcarbonyl.

As C_{1-6} alkoxycarbonyl groups, there may be mentioned methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, i-propoxycarbonyl, n-butoxycarbonyl, i-butoxycarbonyl, s-butoxycarbonyl, t-butoxycarbonyl, 1-pentyloxycarbonyl, 2-pentyloxycarbonyl, 3-pentyloxycarbonyl, i-pentyloxycarbonyl, neopentyloxycarbonyl, t-pentyloxycarbonyl, 1-hexyloxycarbonyl, 2-hexyloxycarbonyl and 3-hexyloxycarbonyl, etc.

Preferably, there may be mentioned methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, i-propoxycarbonyl, n-butoxycarbonyl, i-butoxycarbonyl, s-butoxycarbonyl and t-butoxycarbonyl.

As C_{1-6} alkylsulfonyl groups, there may be mentioned methanesulfonyl and ethanesulfonyl.

As arylcarbonyl groups, there may be mentioned benzoyl, p-methylbenzoyl, p-t-butylbenzoyl, p-methoxybenzoyl, p-chlorobenzoyl, p-nitrobenzoyl and p-cyanobenzoyl.

Preferably, there may be mentioned benzoyl, p-nitrobenzoyl and p-cyanobenzoyl.

As C_{3-6} cycloalkyl groups, there may be mentioned cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl, etc.

Preferably, there may be mentioned cyclopropyl, cyclobutyl

and cyclohexyl.

As preferable compounds used in the present invention, the following compounds may be mentioned.

(1) A benzopyran derivative of the formula (I) or pharmaceutically acceptable salt thereof, wherein R^1 and R^2 represent both methyl groups, R^3 represents a hydroxyl group and R^4 represents a hydrogen atom.

(2) A benzopyran derivative or pharmaceutically acceptable salt thereof according to the aforementioned (1), wherein R^9 represents a hydrogen atom or a nitro group.

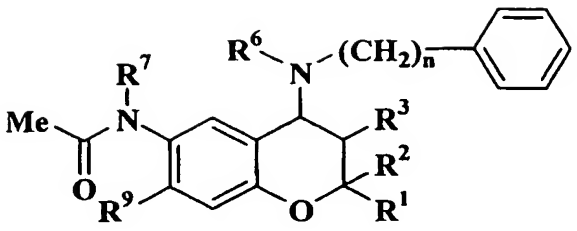
(3) A benzopyran derivative or pharmaceutically acceptable salt thereof according to the aforementioned (2), wherein X represents C=O, and R^6 and R^7 represent both hydrogen atoms.

(4) A benzopyran derivative or pharmaceutically acceptable salt thereof according to the aforementioned (3), wherein R^5 represents a benzene ring, Y is absent, m represents 0, and n represents 1 or 2.

(5) A benzopyran derivative or pharmaceutically acceptable salt thereof according to the aforementioned (4), wherein R^8 represents an alkyl group, R^9 represents a nitro group, and n represents 2.

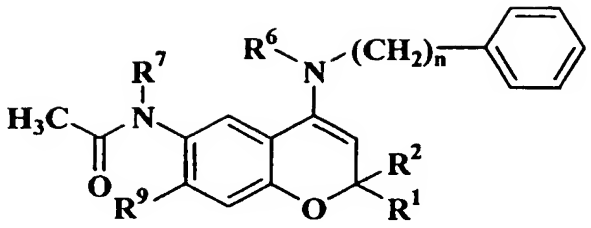
Specific examples of the compounds that can be used in the present invention are shown as follows, but the present invention is not limited thereto. Herein, "Me" means a methyl group, "Et" means an ethyl group, "Pr" means a propyl group, "Bu" means a butyl group, "Pen" means an pentyl group, "Hex" means a hexyl group, "Ph" means a phenyl group, "Ac" means an acetyl group ($COCH_3$), and "-" means a bond, respectively.

Table 1



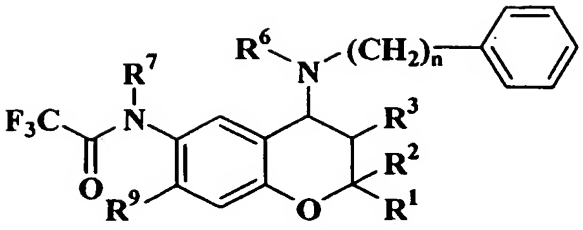
R^1	R^2	R^3	R^6	R^7	R^9	n
H	H	OH	H	H	H	0
Me	Me	OH	Me	H	H	1
Me	Me	OH	Et	H	H	2
Me	Me	OH	n-Pr	H	H	3
Me	Me	OH	i-Pr	H	H	4
Me	Me	OH	n-Bu	H	H	0
Me	Me	OH	i-Bu	H	H	1
Me	Me	OH	t-Bu	H	H	2
Me	Me	OH	n-Pen	H	H	3
Me	Me	OH	n-Hex	H	H	4
Me	Me	OH	H	H	H	2
Me	Me	OH	Me	H	H	2
Me	Me	OH	Et	H	H	3
Me	Me	OCOMe	H	H	H	2
Me	Me	OCOEt	H	H	NO_2	2
Me	Me	OH	H	H	NO_2	2
Me	Me	OH	H	H	NO_2	3
Me	Me	OH	H	H	NO_2	4
Ph	Ph	OH	H	i-Pr	NO_2	4
Et	Et	OH	H	n-Bu	NO_2	2
n-Pr	n-Pr	OH	H	i-Bu	NO_2	2
i-Pr	i-Pr	OH	H	t-Bu	NO_2	2
n-Bu	n-Bu	OH	H	n-Pen	NO_2	2
i-Bu	i-Bu	OH	H	n-Hex	NO_2	2
t-Bu	t-Bu	OH	H	Me	NO_2	3
n-Pen	n-Pen	OH	H	H	Cl	3
n-Hex	n-Hex	OH	H	H	F	3
CF_3	CF_3	OH	H	H	Br	3
CH_2OCH_3	CH_2OCH_3	OH	H	H	CN	3

Table 2



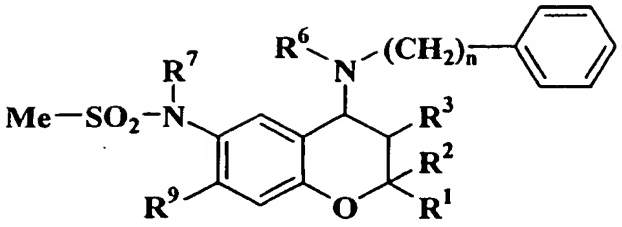
R^1	R^2	R^6	R^7	R^9	n
H	H	H	H	H	0
Me	Me	Me	H	H	1
Me	Me	Et	H	H	2
Me	Me	n-Pr	H	H	3
Me	Me	i-Pr	H	H	4
Me	Me	n-Bu	H	H	0
Me	Me	i-Bu	H	H	1
Me	Me	t-Bu	H	H	2
Me	Me	n-Pen	H	H	3
Me	Me	n-Hex	H	H	4
Me	Me	H	H	H	2
Me	Me	Me	H	H	2
Me	Me	Et	H	H	3
Me	Me	H	H	H	2
Me	Me	H	H	NO_2	2
Me	Me	H	Me	NO_2	1
Me	Me	H	Et	NO_2	2
Me	Me	H	n-Pr	NO_2	3
Ph	Ph	H	i-Pr	NO_2	4
Et	Et	H	n-Bu	NO_2	2
n-Pr	n-Pr	H	i-Bu	NO_2	2
i-Pr	i-Pr	H	t-Bu	NO_2	2
n-Bu	n-Bu	H	n-Pen	NO_2	2
i-Bu	i-Bu	H	n-Hex	NO_2	2
t-Bu	t-Bu	H	Me	NO_2	3
n-Pen	n-Pen	H	H	Cl	3
n-Hex	n-Hex	H	H	F	3
CF_3	CF_3	H	H	Br	3
CH_2OCH_3	CH_2OCH_3	H	H	CN	3

Table 3



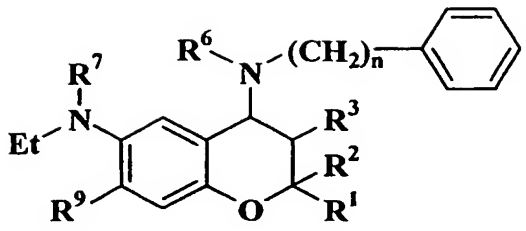
R^1	R^2	R^3	R^6	R^7	R^9	n
H	H	OH	H	H	H	0
Me	Me	OH	Me	H	H	1
Me	Me	OH	Et	H	H	2
Me	Me	OH	n-Pr	H	H	3
Me	Me	OH	i-Pr	H	H	4
Me	Me	OH	n-Bu	H	H	0
Me	Me	OH	i-Bu	H	H	1
Me	Me	OH	t-Bu	H	H	2
Me	Me	OH	n-Pen	H	H	3
Me	Me	OH	n-Hex	H	H	4
Me	Me	OH	H	H	H	2
Me	Me	OH	Me	H	H	2
Me	Me	OH	Et	H	H	3
Me	Me	OCOMe	H	H	H	2
Me	Me	OCOEt	H	H	NO_2	2
Me	Me	OH	H	Me	NO_2	1
Me	Me	OH	H	Et	NO_2	2
Me	Me	OH	H	n-Pr	NO_2	3
Ph	Ph	OH	H	i-Pr	NO_2	4
Et	Et	OH	H	n-Bu	NO_2	2
n-Pr	n-Pr	OH	H	i-Bu	NO_2	2
i-Pr	i-Pr	OH	H	t-Bu	NO_2	2
n-Bu	n-Bu	OH	H	n-Pen	NO_2	2
i-Bu	i-Bu	OH	H	n-Hex	NO_2	2
t-Bu	t-Bu	OH	H	Me	NO_2	3
n-Pen	n-Pen	OH	H	H	Cl	3
n-Hex	n-Hex	OH	H	H	F	3
CF_3	CF_3	OH	H	H	Br	3
CH_2OCH_3	CH_2OCH_3	OH	H	H	CN	3

Table 4



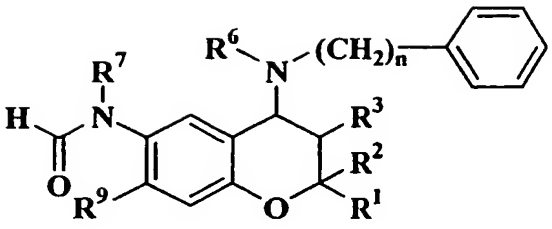
R^1	R^2	R^3	R^6	R^7	R^9	n
H	H	OH	H	H	H	0
Me	Me	OH	Me	H	H	1
Me	Me	OH	Et	H	H	2
Me	Me	OH	n-Pr	H	H	3
Me	Me	OH	i-Pr	H	H	4
Me	Me	OH	n-Bu	H	H	0
Me	Me	OH	i-Bu	H	H	1
Me	Me	OH	t-Bu	H	H	2
Me	Me	OH	n-Pen	H	H	3
Me	Me	OH	n-Hex	H	H	4
Me	Me	OH	H	H	H	2
Me	Me	OH	Me	H	H	2
Me	Me	OH	Et	H	H	3
Me	Me	OCOMe	H	H	H	2
Me	Me	OCOEt	H	H	NO_2	2
Me	Me	OH	H	Me	NO_2	1
Me	Me	OH	H	Et	NO_2	2
Me	Me	OH	H	n-Pr	NO_2	3
Ph	Ph	OH	H	i-Pr	NO_2	4
Et	Et	OH	H	n-Bu	NO_2	2
n-Pr	n-Pr	OH	H	i-Bu	NO_2	2
i-Pr	i-Pr	OH	H	t-Bu	NO_2	2
n-Bu	n-Bu	OH	H	n-Pen	NO_2	2
i-Bu	i-Bu	OH	H	n-Hex	NO_2	2
t-Bu	t-Bu	OH	H	Me	NO_2	3
n-Pen	n-Pen	OH	H	H	Cl	3
n-Hex	n-Hex	OH	H	H	F	3
CF_3	CF_3	OH	H	H	Br	3
CH_2OCH_3	CH_2OCH_3	OH	H	H	CN	3

Table 5



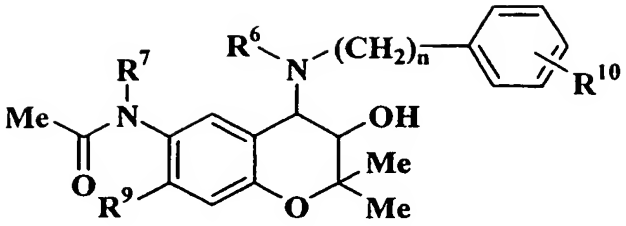
R^1	R^2	R^3	R^6	R^7	R^9	n
H	H	OH	H	H	H	0
Me	Me	OH	Me	H	H	1
Me	Me	OH	Et	H	H	2
Me	Me	OH	n-Pr	H	H	3
Me	Me	OH	i-Pr	H	H	4
Me	Me	OH	n-Bu	H	H	0
Me	Me	OH	i-Bu	H	H	1
Me	Me	OH	t-Bu	H	H	2
Me	Me	OH	n-Pen	H	H	3
Me	Me	OH	n-Hex	H	H	4
Me	Me	OH	H	H	H	2
Me	Me	OH	Me	H	H	2
Me	Me	OH	Et	H	H	3
Me	Me	OCOMe	H	H	H	2
Me	Me	OCOEt	H	H	NO_2	2
Me	Me	OH	H	Me	NO_2	1
Me	Me	OH	H	Et	NO_2	2
Me	Me	OH	H	n-Pr	NO_2	3
Ph	Ph	OH	H	i-Pr	NO_2	4
Et	Et	OH	H	n-Bu	NO_2	2
n-Pr	n-Pr	OH	H	i-Bu	NO_2	2
i-Pr	i-Pr	OH	H	t-Bu	NO_2	2
n-Bu	n-Bu	OH	H	n-Pen	NO_2	2
i-Bu	i-Bu	OH	H	n-Hex	NO_2	2
t-Bu	t-Bu	OH	H	Me	NO_2	3
n-Pen	n-Pen	OH	H	H	Cl	3
n-Hex	n-Hex	OH	H	H	F	3
CF_3	CF_3	OH	H	H	Br	3
CH_2OCH_3	CH_2OCH_3	OH	H	H	CN	3

Table 6



R^1	R^2	R^3	R^6	R^7	R^9	n
H	H	OH	H	H	H	0
Me	Me	OH	Me	H	H	1
Me	Me	OH	Et	H	H	2
Me	Me	OH	n-Pr	H	H	3
Me	Me	OH	i-Pr	H	H	4
Me	Me	OH	n-Bu	H	H	0
Me	Me	OH	i-Bu	H	H	1
Me	Me	OH	t-Bu	H	H	2
Me	Me	OH	n-Pen	H	H	3
Me	Me	OH	n-Hex	H	H	4
Me	Me	OH	H	H	H	2
Me	Me	OH	Me	H	H	2
Me	Me	OH	Et	H	H	3
Me	Me	OCOMe	H	H	H	2
Me	Me	OCOEt	H	H	NO_2	2
Me	Me	OH	H	Me	NO_2	1
Me	Me	OH	H	Et	NO_2	2
Me	Me	OH	H	n-Pr	NO_2	3
Ph	Ph	OH	H	i-Pr	NO_2	4
Et	Et	OH	H	n-Bu	NO_2	2
n-Pr	n-Pr	OH	H	i-Bu	NO_2	2
i-Pr	i-Pr	OH	H	t-Bu	NO_2	2
n-Bu	n-Bu	OH	H	n-Pen	NO_2	2
i-Bu	i-Bu	OH	H	n-Hex	NO_2	2
t-Bu	t-Bu	OH	H	Me	NO_2	3
n-Pen	n-Pen	OH	H	H	Cl	3
n-Hex	n-Hex	OH	H	H	F	3
CF_3	CF_3	OH	H	H	Br	3
CH_2OCH_3	CH_2OCH_3	OH	H	H	CN	3

Table 7



R^6	R^7	R^9	R^{10}	n
H	H	H	p-MeO	0
Me	H	H	p-MeO	1
H	H	NO_2	p-MeO	2
n-Pr	H	H	p-MeO	3
i-Pr	H	H	p-MeO	4
n-Bu	H	H	m-MeO	0
i-Bu	H	H	o-MeO	1
t-Bu	H	H	p-Me	2
n-Pen	H	H	p-Et	3
n-Hex	H	H	m-Et	4
H	H	H	o-Et	2
H	H	NO_2	p-Cl	2
Et	H	H	p-F	3
H	H	NO_2	p-OH	2
H	H	NO_2	p-OH	2
H	Me	NO_2	p-NO_2	1
H	Et	NO_2	p-CN	2
H	n-Pr	NO_2	p-NMe_2	3
H	i-Pr	NO_2	p-NHMe	4
H	n-Bu	NO_2	p-CO_2H	2
H	i-Bu	NO_2	m-CO_2Et	2
H	t-Bu	NO_2	m-OMe	2
H	H	NO_2	p-NO_2	2
H	n-Hex	NO_2	p-NMe_2	2
H	Me	NO_2	p-NHMe	3
H	H	NO_2	p-NH_2	2
H	H	F	p-Et	3
H	H	Br	p-Pr	3
H	H	CN	p-CH_2OMe	3

The compound according to the present invention has asymmetric carbon atoms at 3-position and 4-positon, thus optical isomers thereof based on the asymmetric carbon atoms are present, which can be used in the application of the present invention similar to racemate thereof. Further, a cis or trans isomer based on configuration at 3-position and 4-position may be included, but the trans isomer is preferable.

Further, when the compounds can form their salts, the pharmaceutically acceptable salts can be also used as active ingredients.

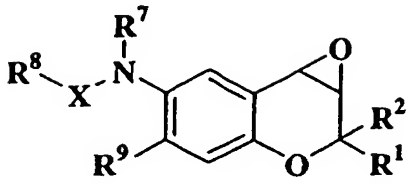
As pharmaceutically acceptable salts, there may be mentioned hydrochlorides, hydrobromides, sulfates, methanesulfonates, acetates, benzoates, tartrates, phosphates, lactates, maleates, fumarates, malates, gluconates and salicylates, etc.

Preferably, there may be mentioned hydrochlorides and methanesulfonates.

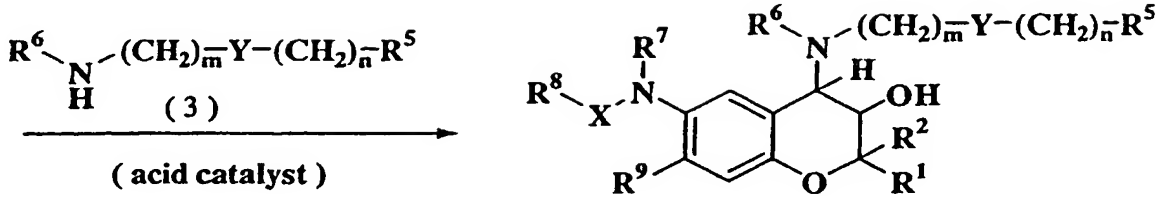
Then, the preparation method of the compound according to the present invention is illustrated.

Of the compounds of the formula (I), those wherein R^4 represents a hydrogen atom and R^3 represents a hydroxyl group, which are the compounds of formula (I-a), can be obtained by reacting a compound of the general formula (2) with a compound (3) in an inert solvent, as shown in the following reaction scheme.

The compound of the general formula (2) can be synthesized according to known methods (methods described in J.M. Evans et al., J. Med. Chem. 1984, 27, 1127, J. Med. Chem. 1986, 29, 2194, J.T. North et al., J. Org. Chem. 1995, 60, 3397, as well as Japanese Patent Application Laid-Open No. Sho 56-57785, Japanese Patent Application Laid-Open No. Sho 56-57786, Japanese Patent Application Laid-Open No. Sho 58-188880, Japanese Patent Application Laid-Open No. Hei 2-141, Japanese Patent Application Laid-Open No. Hei 10-87650 and Japanese Patent Application Laid-Open No. Hei 11-209366, etc.).



(2)



(I-a)

In this scheme, R^1, R^2, R^5, R^6, R^7, R^8, R^9, X, Y, m and n are as defined above.

As the solvents used in the reaction of the compound of the general formula (2) with the compound (3), the following may be mentioned.

There may be mentioned sulfoxide type solvents exemplified by dimethylsulfoxide; amide type solvents exemplified by dimethylformamide or dimethylacetamide; ether type solvents exemplified by ethyl ether, dimethoxyethane or tetrahydrofuran; halogen type solvents exemplified by dichloromethane, chloroform and dichloroethane; nitrile type solvents exemplified by acetonitrile and propionitrile; aromatic hydrocarbon type solvents exemplified by benzene and toluene; hydrocarbon type solvents exemplified by hexane and heptane; and ester type solvents exemplified by ethyl acetate. Further, the reaction can be carried out in the absence of a solvent. Preferably, ether type solvents and nitrile type solvents may be mentioned.

The reaction temperature is generally from -80°C to the reflux temperature of the reaction solvent, preferably from -10°C to 100°C.

The molar ratio of the reaction materials is within the range of 0.5-20.0, preferably 1.0-10.0, for the compound (3)/the compound (2).

An acid catalyst may be used in the reaction.

As the acid catalysts used, there may be mentioned inorganic

acids exemplified by hydrochloric acid and sulfuric acid, as well as Lewis acids exemplified by aluminum chloride, titanium tetrachloride, boron trifluoride diethyl ether complex, perchloric acid, lithium perchlorate, lithium bromide and ytterbium trifluoromethanesulfonate, etc.

Of the compounds of the general formula (I), those other than the compounds of formula (I-a) described above (those of the formula (I) wherein R^3 and R^4 together form a bond and those of the formula (I) wherein R^4 represents a hydrogen atom and R^3 represents a C_{1-6} alkylcarbonyloxy group) can be prepared by the methods similar to those described in Japanese Patent Application Laid-Open No. Sho 52-91866 and Japanese Patent Application Laid-Open No. Hei 10-87650, etc.

Preferably, there may be mentioned lithium bromide, perchloric acid and lithium perchlorate.

Syntheses of optically active compounds included in the compounds of the general formula (I) can be attained by utilizing optical resolution methods (Japanese Patent Application Laid-Open No. Hei 3-141286, U.S. Patent No. 5097037 and European Patent No. 409165). Further, syntheses of optically active compounds of the general formula (2) can be attained by utilizing asymmetrical synthetic methods (Japanese National Publication No. Hei 5-507645, Japanese Patent Application Laid-Open No. Hei 5-301878, Japanese Patent Application Laid-Open No. Hei 7-285983, European Patent Application Laid-open No.535377, and U.S. Patent No. 5420314).

As described above, we, inventors, found that the compound of the general formula (I) has the strong prolongation effect on the functional refractory period. The prolongation effect on the functional refractory period is one of the functions of antiarrhythmic action and an important indicator that can be extrapolated to efficiency for clinical arrhythmia. Conventional antiarrhythmic agents having the prolongation effect on the functional refractory period as the main function (such as d-sotalol belonging to Class III of the antiarrhythmic agent classification according to Vaughan Williams) have quite dangerous arrhythmic inducing actions that can result in sudden death such as torsades

de pointes based on extension of ventricular muscle action potential relating to the prolongation effect on the functional refractory period, which become the therapeutic problems for arrhythmia based on atrium (such as supraventricular tachycardia, atrial flutter and atrial fibrillation). In order to solve the problems, we, inventors, carried out searching and studying of compounds having the prolongation effect on the functional refractory period more selective for atrium muscle than for ventricular muscle, and found that the compound of the general formula (I) has the prolongation effect on the functional refractory period selective for atrium muscle without any influence on the functional refractory period of ventricular muscle and action potential. The difference between the present invention by the inventors and the known techniques is to provide the prolongation effect on the functional refractory period selective for atrium muscle by the compound, which is shown by the following facts; without any influence on the action potential sustaining period of removed ventricular muscle and without any influence on the electrocardiogram QT of anesthetized animal. From the above, the compounds of the present invention have no arrhythmic inducing action in ventricular muscle, thus they can provide possibilities of more safe uses for arrhythmia based on atrium muscle than known techniques. The technique according to the present invention is useful for therapeutic or preventive uses as anti-atrial fibrillation agents, anti-atrial flutter agents and anti-atrial tachycardia agents relating to paroxysmal, chronic, preoperative, intraoperative or postoperative atrial arrhythmia, prevention of proceeding to embolus based on atrial arrhythmia, prevention of proceeding to ventricular arrhythmia or tachycardia originated from atrial arrhythmia or tachycardia, and prevention of the life prognosis worsening based on the preventive action for atrial arrhythmia or tachycardia which can be proceeded to ventricular arrhythmia or tachycardia.

The present invention provides a pharmaceutical composition or veterinary pharmaceutical composition containing the compound of the generally formula (I) in an effective amount for these treatments.

As administering forms of the compound according to the present invention, there may be mentioned parenteral administrations by means of injections (subcutaneous, intravenous, intramuscular and intraperitoneal injections), ointments, suppositories and aerosol, or oral administrations by means of tablets, capsules, granules, pills, syrups, solutions, emulsions and suspensions, etc.

The above-mentioned pharmaceutical or veterinary pharmaceutical composition contains the compound according to the present invention in an amount of about 0.01-99.5%, preferably about 0.1-30%, of the total composition weight.

In addition to the compound according to the present invention or the composition containing the compound, other pharmaceutically or veterinary pharmaceutically active compounds may be contained.

Further, these compositions may contain the plurality of compounds according to the present invention.

A clinical administration amount varies depending on age, weight and sensitivity of the patient, extent of condition of the patient, etc. and an effective administration amount is generally about 0.003-1.5 g, preferably 0.01-0.6 g, per day for adult. If necessary, however, the amount outside of the above-mentioned range may be used.

The compound according to the present invention is formulated for administration by conventional pharmaceutical means.

That is, tablets, capsules, granules and pills for oral administration are prepared by using excipients such as sucrose, lactose, glucose, starch and mannitol; binders such as hydroxypropyl cellulose, syrup, gum arabic, gelatin, sorbitol, tragacanth, methyl cellulose and polyvinyl pyrrolidone; disintegrators such as starch, carboxymethyl cellulose or its calcium salt, microcrystalline cellulose and polyethylene glycol; lubricants such as talc, magnesium or calcium stearate, and silica; lubricaing agents such as sodium laurate and glycerol, etc.

Injections, solutions, emulsions, suspensions, syrups and aerosols are prepared by using solvents for the active components such as water, ethyl alcohol, isopropyl alcohol, propylene glycol,

1,3-butylene glycol and polyethylene glycol; surfactants such as sorbitan fatty acid ester, polyoxyethylene sorbitan fatty acid ester, polyoxyethylene fatty acid ester, polyoxyethylene ether of hydrogenated castor oil and lecithin; suspending agents such as carboxymethyl sodium salt, cellulose derivatives such as methyl cellulose, tragacanth, and natural rubbers such as gum arabic; and preserves such as p-hydroxybenzoic acid esters, benzalkonium chloride and sorbic acid salts, etc.

For ointments that are transdermally adsorptive pharmaceutics, white vaseline, liquid paraffin, higher alcohols, Macrogol ointments, hydrophilic ointments and aqueous gel-type bases are, for example, used.

Suppositories are prepared by using, for example, cocoa fats, polyethylene glycol, lanolin, fatty acid triglyceride, coconut oil and Polysorbate etc.

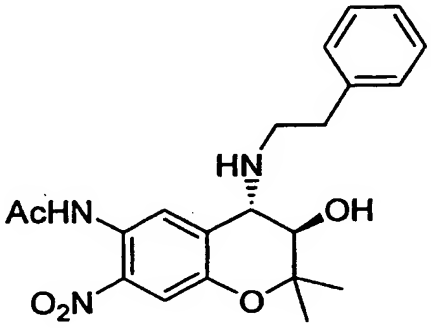
Best Mode for Carrying Out the Invention

The present invention is illustrated in detail by the Examples as follows, but the present invention is not limited to these Examples.

[Synthesis Examples]

Synthesis example 1

Trans-6-acetylamino-3,4-dihydro-2,2-dimethyl-7-nitro-4-(2-phenetylamino)-2H-1-benzopyran-3-ol



To a solution of 6-acetylamino-3,4-epoxy-3,4-dihydro-2,2-dimethyl-7-nitro-2H-1-benzopyran (500 mg, 1.80 mmol) and lithium

perchlorate (766 mg, 7.20 mmol) in tetrahydrofuran (15 mL), 2-phenetylamine (904 µL, 7.20 mmol) was added at the room temperature and stirred at 65°C for 9 hours.

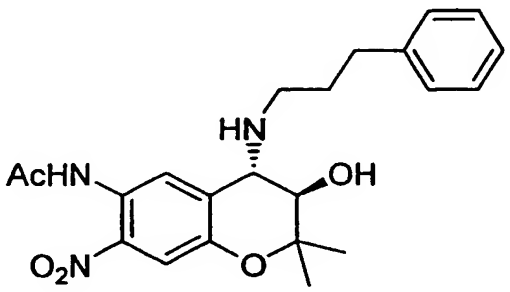
Thereto, ethyl acetate was added, and the formed organic phase was washed twice with an aqueous saturated ammonium chloride solution and once with an aqueous saturated sodium chloride solution, and dried over anhydrous magnesium sulfate.

After the solvent was distilled off, the residue was purified by medium-pressure column chromatography (hexane: ethyl acetate = 1:1) and thereafter recrystallized from hexane - ethyl acetate, to obtain the intended substance as yellow crystals (yield; 61%).
mp. : 172-174 °C
^{1}H-NMR ($CDCl_3$) δ : 1.17 (s, 3H), 1.48 (s, 3H), 1.60 (br s, 2H), 2.28 (s, 3H), 2.83 (t, J = 7.0 Hz, 2H), 2.85-3.00 (m, 2H), 3.47 (d, A part of AB, J = 10.3 Hz, 1H), 3.67 (d, B part of AB, J = 10.3 Hz, 1H), 7.21-7.33 (m, 5H), 7.60 (s, 1H), 8.59 (s, 1H), 9.96 (s, 1H).
MS (EI) m/z; 400[M+1]$^+$, 327 (bp).

The following compounds were obtained by the similar method (Synthesis examples 2-36).

Synthesis example 2

Trans-6-acetylamino-3,4-dihydro-2,2-dimethyl-7-nitro-4-(3-phenylpropylamino)-2H-1-benzopyran-3-ol

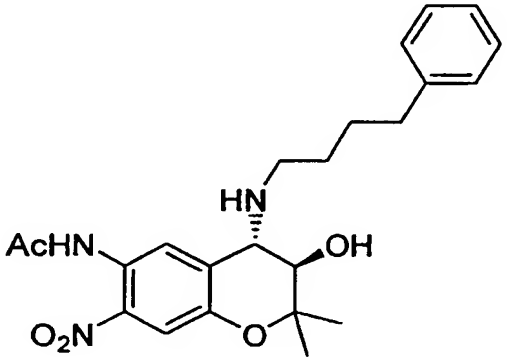


Yield: 71 %
^{1}H-NMR ($CDCl_3$) δ :1.21 (s, 3H), 1.51 (s, 3H), 1.87 (quint, J = 7.4 Hz, 2H), 1.94 (br s, 2H), 2.27 (s, 3H), 2.63-2.73 (m, 4H), 3.54

(d, A part of AB, J = 10.3 Hz, 1H), 3.71 (d, B part of AB, J = 10.3 Hz, 1H), 7.16-7.23 (m, 3H), 7.25-7.27 (m, 2H), 7.63 (s, 1H), 8.68 (s, 1H), 10.02 (s, 1H).
MS (EI) m/z; 413[M]$^+$, 221 (bp).

Synthesis example 3

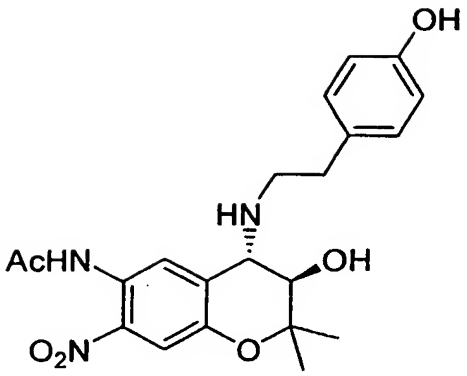
Trans-6-acetylamino-3,4-dihydro-2,2-dimethyl-7-nitro-4-(4-phenylbuthylamino)-2H-1-benzopyran-3-ol



Yield: 50 %
^{1}H-NMR ($CDCl_3$) δ :1.20 (s, 3H), 1.52 (s, 3H), 1.55-1.60 (m, 2H), 1.63-1.75 (m, 2H), 2.25 (s, 3H), 2.40 (br s, 2H), 2.62 (t, J = 7.4 Hz, 2H), 2.58-2.72 (m, 2H), 3.57 (d, A part of AB, J = 10.0 Hz, 1H), 3.70 (d, B part of AB, J = 10.0 Hz, 1H), 7.15-7.18 (m, 3H), 7.24-7.62 (m, 2H), 7.62 (s, 1H), 8.67 (s, 1H), 10.00 (s, 1H).
MS (EI) m/z; 427[M]$^+$, 150 (bp).

Synthesis example 4

Trans-6-acetylamino-3,4-dihydro-2,2-dimethyl-7-nitro-4-[2-(4-hydroxyphenyl)ethylamino]-2H-1-benzopyran-3-ol



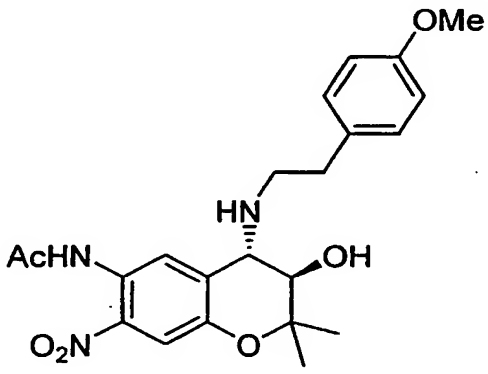
Yield: 29 %

^{1}H-NMR ($CDCl_3$) δ :1.17 (s, 3H), 1.48 (s, 3H), 2.00 (br s, 3H), 2.29 (s, 3H), 2.70-2.85 (m, 3H), 2.86-2.95 (m, 1H), 3.51 (d, A part of AB, J = 10.3 Hz, 1H), 3.66 (d, B part of AB, J = 10.3 Hz, 1H), 6.77 (d, J = 8.4 Hz, 2H), 7.06 (d, J = 8.4 Hz, 2H), 7.60 (s, 1H), 8.46 (s, 1H), 9.95 (s, 1H) .

MS (EI) m/z; 416[M+1]$^+$, 308 (bp).

Synthesis example 5

Trans-6-acetylamino-3,4-dihydro-2,2-dimethyl-7-nitro-4-[2-(4-methoxyphenyl)ethylamino]-2H-1-benzopyran-3-ol



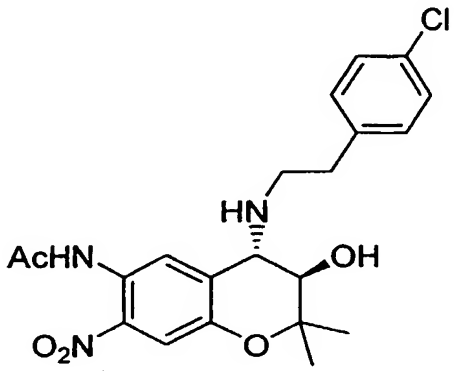
Yield: 18 %

^{1}H-NMR ($CDCl_3$) δ :1.18 (s, 3H), 1.49 (s, 3H), 1.80 (br s, 2H), 2.27 (s, 3H), 2.76-3.00 (m, 4H), 3.56 (d, A part of AB, J = 10.5 Hz, 1H), 3.77 (d, B part of AB, J = 10.5 Hz, 1H), 3.79 (s, 3H), 6.83 (d, J = 8.6 Hz, 2H), 7.23 (d, J = 8.6 Hz, 2H), 7.61 (s, 1H), 8.55 (s, 1H), 9.93 (s, 1H) .

MS (EI) m/z; 430[M+1]$^+$, (bp).

Synthesis example 6

Trans-6-acetylamino-3,4-dihydro-2,2-dimethyl-7-nitro-4-[2-(4-chlorophenyl)ethylamino]-2H-1-benzopyran-3-ol



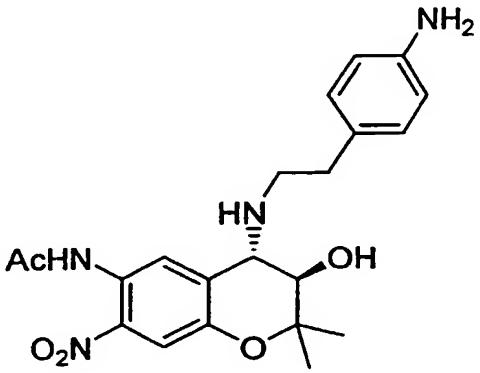
Yield: 66 %

^{1}H-NMR ($CDCl_3$) δ :1.18 (s, 3H), 1.49 (s, 3H), 1.70 (br s, 2H), 2.28 (s, 3H), 2.78 (t, J = 6.8 Hz, 2H), 2.84-2.99 (m, 2H), 3.50 (d, A part of AB, J = 10.2 Hz, 1H), 3.68 (dd, B part of AB, J = 10.2 and 1.0 Hz, 1H), 7.17 (d, J= 8.4 Hz, 2H), 7.27 (d, J = 8.4 Hz, 2H), 7.61 (s, 1H), 8.59 (s, 1H), 9.97 (s, 1H).

MS (EI) m/z; 434[M+1]$^+$, 361 (bp).

Synthesis example 7

Trans-6-acetylamino-3,4-dihydro-2,2-dimethyl-7-nitro-4-[2-(4-aminophenyl)ethylamino]-2H-1-benzopyran-3-ol



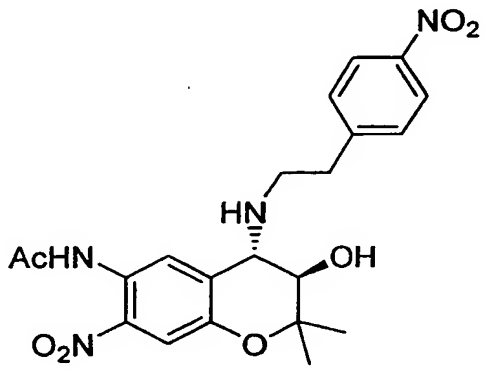
Yield: 40 %

^{1}H-NMR ($CDCl_3$) δ :1.17 (s, 3H), 1.48 (s, 3H), 1.69 (br s, 4H), 2.28 (s, 3H), 2.71 (t, J = 6.8 Hz, 2H), 2.79-2.92 (m, 2H), 3.48 (d, A part of AB, J = 10.3 Hz, 1H), 3.67 (dd, B part of AB, J = 10.3 and 1.1 Hz, 1H), 6.63 (d, J = 8.6 Hz, 2H), 7.02 (d, J = 8.6 Hz, 2H), 7.60 (s, 1H), 8.58 (s, 1H), 9.96 (s, 1H).

MS (EI) m/z; 415[M+1]$^+$, 237(bp).

Synthesis example 8

Trans-6-acetylamino-3,4-dihydro-2,2-dimethyl-7-nitro-4-[2-(4-nitrophenyl)ethylamino]-2H-1-benzopyran-3-ol



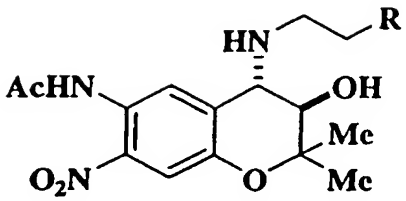
Yield: 19 %

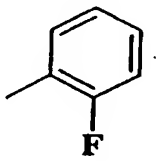
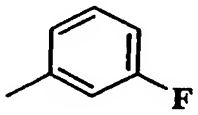
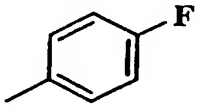
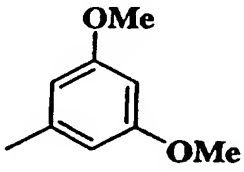
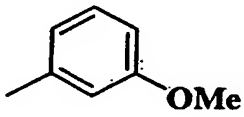
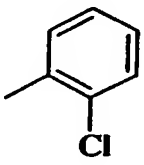
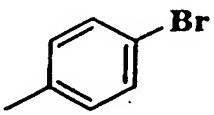
mp.: 211-213 °C (decomposition)

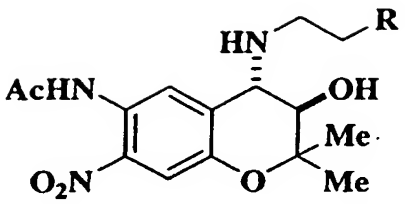
^{1}H-NMR (DMSO-d_6) δ : 1.15 (s, 3H), 1.45 (s, 3H), 2.05 (s, 3H), 3.05-3.40 (m, 5H), 4.06 (m 1H), 4.51 (m, 1H), 6.44 (s, 1H), 7.40 (s, 1H), 7.56 (d, J = 8.8 Hz, 2H), 7.90 (s, 1H), 8.20 (d, J = 8.8 Hz, 2H), 10.14 (s, 1H).

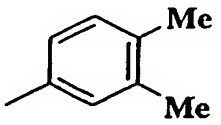
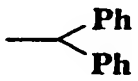
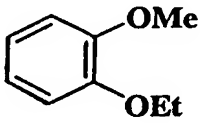
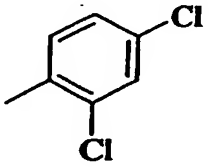
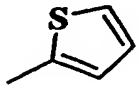
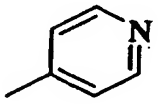
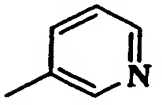
MS (EI) m/z; 444[M]$^+$, 371 (bp).

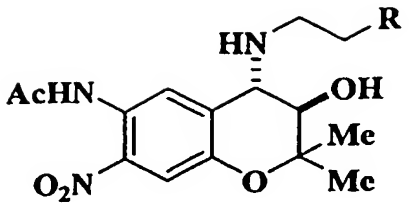
Synthesis examples 9-36

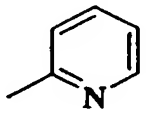
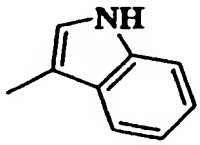
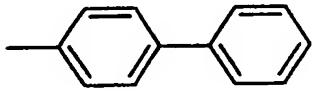
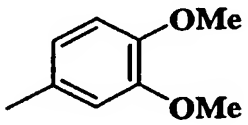
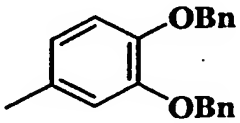
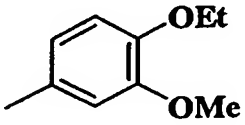
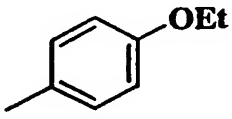


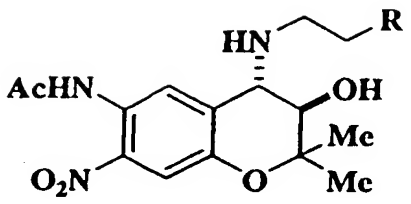
Synthesis example No.	R
9	
10	
11	
12	
13	
14	
15	

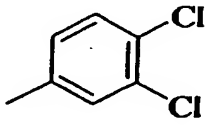
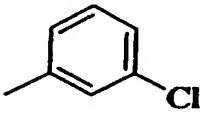
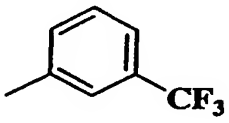
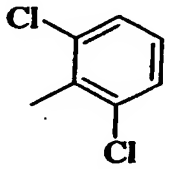


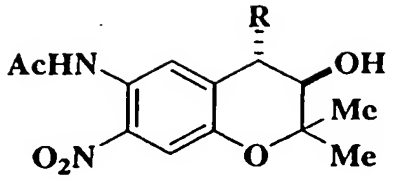
Synthesis example No.	R
16	
17	
18	
19	
20	
21	
22	

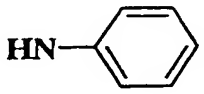
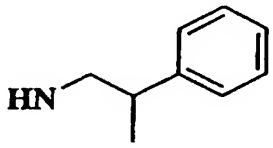
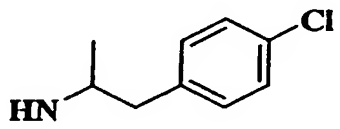


Synthesis example No.	R
23	
24	
25	
26	
27	
28	
29	



Synthesis example No.	R
30	
31	
32	
33	



Synthesis example No.	R
34	
35	
36	

Synthesis example 9

Red crystal

mp. : 176.5-178.0 °C

^{1}H-NMR ($CDCl_3$) δ : 1.17 (s, 3H), 1.48 (s, 3H), 2.27 (s, 3H), 2.86-2.98 (m, 4H), 3.46 (d, J=10.0 Hz, 1H), 3.68 (d, J=10.0 Hz, 1H), 7.00-7.10 (m, 2H), 7.17-7.26 (m, 2H), 7.61 (s, 1H), 8.63 (s, 1H), 9.98 (s, 1H).

MS (EI) m/z; 418[M+1]$^+$, 346, 309, 179 (bp).

Synthesis example 10

Red crystal

mp. : 163.5-165.0 °C

^{1}H-NMR ($CDCl_3$) δ : 1.18 (s, 3H), 1.49 (s, 3H), 2.27 (s, 3H), 2.81-2.99 (m, 4H), 3.49 (d, J=10.1 Hz, 1H), 3.68 (d, J=10.1 Hz, 1H), 6.89-6.95 (m, 2H), 7.02 (d, J= 7.6 Hz, 1H), 7.23-7.26 (m, 1H), 7.61 (s, 1H), 8.58 (s, 1H), 9.96 (s, 1H).

MS (EI) m/z; 418[M+1]$^+$, 344, 298 (bp).

Synthesis example 11

Orange crystal

mp. : 141.0-142.0 °C

^{1}H-NMR ($CDCl_3$) δ : 1.18 (s, 3H), 1.49 (s, 3H), 2.27 (s, 3H), 2.78-2.97 (m, 4H), 3.49 (d, J = 10.1 Hz, 1H), 3.68 (d, J = 10.1 Hz, 1H), 6.99 (t, J = 8.8 Hz, 2H), 7.19 (dd, J = 2.9, 5.5 Hz, 2H), 7.61 (s, 1H), 8.57 (s, 1H), 9.97 (s, 1H).

MS (EI) m/z; 417[M]$^+$, 345, 302, 176 (bp).

Synthesis example 12

Yellow crystal

mp. : 151.0-152.0 °C

^{1}H-NMR ($CDCl_3$) δ : 1.18 (s, 3H), 1.49 (s, 3H), 2.26 (s, 3H), 2.77 (t, J = 6.8 Hz, 2H), 2.87-2.97 (m, 2H), 3.51 (d, J = 10.1 Hz, 1H), 3.69 (d, J = 10.1 Hz, 1H), 6.33 (d, J = 2.2 Hz, 1H), 6.39 (d, J = 2.2 Hz, 2H), 7.60 (s, 1H), 8.55 (s, 1H), 9.93 (s, 1H).

MS (EI) m/z; 459[M]$^+$, 441, 307, 278, 193 (bp).

Synthesis example 13

Red amorphous substance

^{1}H-NMR ($CDCl_3$) δ : 1.18 (s, 3H), 1.48 (s, 3H), 2.27 (s, 3H), 2.78-2.97 (m, 4H), 3.50 (d, J = 10.1 Hz, 1H), 3.69 (d, J = 10.1 Hz, 1H), 3.79 (s, 3H), 6.75-6.83 (m, 3H), 7.21 (t, J = 7.6 Hz, 1H), 7.60 (s, 1H), 8.56 (s, 1H), 9.94 (s, 1H).

MS (FAB) m/z; 430[M+1]$^+$ (bp).

Synthesis example 14

Red crystal

mp. : 171.5-172.8 °C

^{1}H-NMR ($CDCl_3$) δ : 1.18 (s, 3H), 1.48 (s, 3H), 2.27 (s, 3H), 2.86-2.98 (m, 4H), 3.48 (d, J=10.4 Hz, 1H), 3.70 (d, J=10.4 Hz, 1H), 7.14-7.22 (m, 2H), 7.26-7.28 (m, 1H), 7.34 (dd, J = 1.6, 7.6 Hz, 1H), 7.61 (s, 1H), 8.64 (s, 1H), 9.98 (s, 1H).

MS (EI) m/z; 433[M+1]$^+$, 357, 318(bp).

Synthesis example 15

Yellow amorphous substance

^{1}H-NMR ($CDCl_3$) δ : 1.18 (s, 3H), 1.49 (s, 3H), 2.28 (s, 3H), 2.79 (t, J = 6.9 Hz, 2H), 2.86-2.98 (m, 2H), 3.50 (d, J = 10.1 Hz, 1H), 3.68 (d, J = 10.1 Hz, 1H), 7.12 (d, J = 8.2 Hz, 2H), 7.42 (d, J = 8.2 Hz, 2H), 7.61 (s, 1H), 8.60 (s, 1H), 9.98 (s, 1H).

MS (EI) m/z; 481[M+2]$^+$, 479[M]$^+$, 406 (bp).

Synthesis example 16

Orange crystal

mp. : 90.0-91.0 °C

^{1}H-NMR ($CDCl_3$) δ : 1.18 (s, 3H), 1.48 (s, 3H), 2.22 (s, 3H), 2.24 (s, 3H), 2.27 (s, 3H), 2.75-2.78 (m, 2H), 2.88-2.91 (m, 2H), 3.50 (d, J = 10.1 Hz, 1H), 3.69 (d, J = 10.1 Hz, 1H), 6.96 (d, J = 7.7 Hz, 1H), 7.00 (s, 1H), 7.06 (d, J = 7.7 Hz, 1H), 7.60 (s, 1H), 8.61 (s, 1H), 9.97 (s, 1H).

MS (EI) m/z; 428[M+1]$^+$, 356 (bp).

Synthesis example 17

Brown amorphous substance

^{1}H-NMR ($CDCl_3$) δ : 1.16 (s, 3H), 1.48 (s, 3H), 2.29 (s, 3H), 2.82 (brs, 1H), 3.25 (dd, J = 2.1, 7.7 Hz, 2H), 3.52 (d, J = 10.3 Hz, 1H), 3.69 (d, J = 10.3 Hz, 1H), 7.18-7.35 (m, 10H), 7.61 (s, 1H), 8.61 (s, 1H), 9.98 (s, 1H).

MS (EI) m/z; 475[M+1]$^+$, 310, 280 (bp).

Synthesis example 18

Yellow crystal

mp. 186.0-188.0 °C

^{1}H-NMR ($CDCl_3$) δ : 1.18 (s, 3H), 1.46 (t, J = 7.1 Hz, 3H), 1.49 (s, 3H), 2.27 (s, 3H), 2.78-3.02 (m, 4H), 3.55 (d, J = 10.3 Hz, 1H), 3.76 (d, J = 10.3 Hz, 1H), 4.11 (q, J = 7.1 Hz, 2H), 6.76-6.82 (m, 3H), 7.61 (s, 1H), 8.53 (s, 1H), 9.93 (s, 1H).

MS (EI) m/z; 473[M+1]$^+$, 440, 401, 308 (bp).

Synthesis example 19

Brown amorphous substance

^{1}H-NMR ($CDCl_3$) δ : 1.19 (s, 3H), 1.49 (s, 3H), 2.27 (s, 3H), 2.84-2.95 (m, 4H), 3.51 (d, J = 10.4 Hz, 1H), 3.71 (d, J = 10.4 Hz, 1H), 7.18 (dd, J = 2.0, 8.0 Hz, 1H), 7.22 (d, J = 8.0 Hz, 1H), 7.36 (d, J = 2.0 Hz, 1H), 7.61 (s, 1H), 8.63 (s, 1H), 9.99 (s, 1H).

MS (EI) m/z; 468[M]$^+$, 396, 353 (bp).

Synthesis example 20

Red crystal

mp. : 156.0-157.0 °C

^{1}H-NMR ($CDCl_3$) δ : 1.19 (s, 3H), 1.50 (s, 3H), 2.28 (s, 3H), 2.93-3.04 (m, 4H), 3.52 (d, J = 10.1 Hz, 1H), 3.71 (d, J = 10.1 Hz, 1H), 6.88 (d, J = 3.3 Hz, 1H), 6.95 (dd, J = 3.3, 5.1 Hz, 1H), 7.16 (d, J = 5.1 Hz, 1H), 7.62 (s, 1H), 8.64 (s, 1H), 9.98 (s, 1H).

MS (EI) m/z; 405[M]$^+$, 332, 308 (bp).

Synthesis example 21

Brown crystal

mp. : 172.0-174.0 °C

^{1}H-NMR ($CDCl_3$) δ : 1.19 (s, 3H), 1.49 (s, 3H), 2.28 (s, 3H), 2.84 (t, J = 6.6 Hz, 2H), 2.90-3.03 (m, 2H), 3.53 (d, J = 10.1 Hz, 1H), 3.71 (d, J = 10.1 Hz, 1H), 7.18 (d, J = 5.9 Hz, 2H), 7.62 (s, 1H), 8.49 (d, J = 5.9 Hz, 2H), 8.64 (s, 1H), 9.98 (s, 1H).

MS (FAB) m/z; 401[M+1]$^+$, 171, 157 (bp).

Synthesis example 22

Brown amorphous substance

^{1}H-NMR ($CDCl_3$) δ : 1.20 (s, 3H), 1.49 (s, 3H), 2.28 (s, 3H), 2.80-2.87 (m, 3H), 2.93-2.96 (m, 1H), 3.58 (d, J = 10.3 Hz, 1H), 3.75 (d, J = 10.3 Hz, 1H), 7.24 (m, 1H), 7.60 (s, 1H), 7.62 (d, J = 1.5 Hz, 1H), 8.42 (t, J = 1.5 Hz, 2H), 8.67 (s, 1H), 9.96 (s, 1H).

MS (EI) m/z; 400[M]$^+$, 328, 280 (bp).

Synthesis example 23

Orange crystal

mp. : 147.0-149.0 °C

^{1}H-NMR ($CDCl_3$) δ : 1.24 (s, 3H), 1.54 (s, 3H), 2.26 (s, 3H), 2.94-3.07 (m, 2H), 3.19-3.21 (m, 2H), 3.66 (d, J = 10.1 Hz, 1H), 3.76 (d, J = 10.1 Hz, 1H), 7.16-7.19 (m, 1H), 7.22 (d, J = 7.7 Hz, 1H), 7.58 (s, 1H), 7.63-7.68 (m, 1H), 8.53 (s, 1H), 8.71 (s, 1H), 9.94 (s, 1H).

MS (FAB) m/z; 400[M]$^+$, 366, 328, 120 (bp).

Synthesis example 24

Brown amorphous substance

^{1}H-NMR ($CDCl_3$) δ : 1.14 (s, 3H), 1.45 (s, 3H), 2.24 (s, 3H), 2.91-3.02 (m, 4H), 3.51 (d, J = 10.3 Hz, 1H), 3.67 (d, J = 10.3 Hz, 1H), 7.10 (t, J = 7.0 Hz, 1H), 7.14 (d, J = 2.2 Hz, 1H), 7.20 (t, J = 7.0 Hz, 1H), 7.37 (d, J = 8.1 Hz, 1H), 7.57 (d, J = 8.1 Hz, 1H), 7.59 (s, 1H), 8.10 (brs, 1H), 8.43 (s, 1H), 9.82 (s, 1H).

MS (FAB) m/z; 437[M-1]$^+$, 307, 278, 233, 194 (bp).

Synthesis example 25

Brown amorphous substance

^{1}H-NMR ($CDCl_3$) δ : 1.18 (s, 3H), 1.49 (s, 3H), 2.23 (s, 3H), 2.87 (t, J = 6.8 Hz, 2H), 2.94-2.99 (m, 2H), 3.52 (d, J = 10.1 Hz, 1H), 3.70 (d, J = 10.1 Hz, 1H), 7.30-7.35 (m, 3H), 7.41-7.45 (m, 2H), 7.52-7.59 (m, 4H), 7.60 (s, 1H), 8.61 (s, 1H), 9.96 (s, 1H).

MS (EI) m/z; 475[M]$^+$, 442, 401 (bp).

Synthesis example 26

Red amorphous substance

^{1}H-NMR ($CDCl_3$) δ : 1.19 (s, 3H), 1.49 (s, 3H), 2.26 (s, 3H), 2.76-2.79 (m, 2H), 2.84-2.90 (m, 1H), 2.93-2.98 (m, 1H), 3.53 (d, J = 10.1 Hz, 1H), 3.70 (d, J = 10.1 Hz, 1H), 3.86 (s, 3H), 3.88 (s, 3H), 6.76-6.81 (m, 3H), 7.60 (s, 1H), 8.54 (s, 1H), 9.93 (s, 1H).

MS (EI) m/z; 460[M+1]$^+$, 237, 165 (bp).

Synthesis example 27

Yield: 58 %
Yellow crystal
mp. 225 °C
^{1}H-NMR (DMSO-d_6) δ : 1.15 (s, 3H), 1.45 (s, 3H), 2.04 (s, 3H), 2.90-3.10 (m, 5H), 3.21 (br s, 1H), 4.00-4.05 (m, 1H), 4.47-4.51 (m, 1H), 5.09 (s, 2H), 5.12 (s, 2H), 6.75 (dd, J = 8.2 and 1.8 Hz, 1H), 6.97 (d, J = 8.2 Hz, 1H), 7.03 (d, J = 2.0 Hz, 1H), 7.28-7.46 (m, 11H), 7.96 (s, 1H), 10.20 (s, 1H).
MS (EI) m/z; 611 $[M]^+$ (bp).

Synthesis example 28
Yield: 32 %
Yellow crystal
mp. 227-228 °C
^{1}H-NMR (DMSO-d_6) δ : 1.15 (s, 3H), 1.29 (t, J = 7.0 Hz, 3H), 1.45 (s, 3H), 2.05 (s, 3H), 2.90-3.10 (m, 4H), 3.25 (br s, 1H), 3.74 (s, 3H), 3.96 (q, J = 7.0 Hz, 2H), 4.00-4.05 (br s, 1H), 4.42 (br s, 1H), 6.45 (br s, 1H), 6.73 (dd, J = 8.4 and 2.4 Hz, 1H), 6.85 (d, J = 2.4 Hz, 1H), 6.86 (d, J = 8.4 Hz, 1H), 7.40 (s, 1H), 7.92 (s, 1H), 10.16 (s, 1H).
MS (EI) m/z; 473 $[M]^+$, 233 (bp).

Synthesis example 29
Yield: 40 %
Yellow amorphous substance
^{1}H-NMR ($CDCl_3$) δ : 1.11 (s, 3H), 1.30 (t, J = 7.0 Hz, 3H), 1.91 (s, 3H), 2.00 (s, 3H), 2.45-2.50 (m, 2H), 2.65 (t, J = 7.1 Hz, 2H), 2.75-2.85 (m, 1H), 3.58 (dd, A part of AB, J = 9.6 and 5.3 Hz, 1H), 3.65 (d, B part of AB, J = 9.6 Hz, 1H), 3.97 (q, J = 7.0 Hz, 2H), 5.43 (d, J = 5.3 Hz, 1H), 6.80 (d, J = 8.8 Hz, 2H), 7.10 (d, J = 8.8 Hz, 2H), 7.60 (s, 1H), 8.32 (s, 1H), 9.95 (s, 1H).
MS (EI) m/z; 443 $[M]^+$, 237 (bp).

Synthesis example 30
Yield: 98 %
Yellow crystal

mp. 214-216 °C
MS (EI) m/z; 467 $[M]^+$, 308 (bp).

Synthesis example 31

Yield: 96 %
Orange crystal
mp. 133-134 °C
^{1}H-NMR ($CDCl_3$) δ : 1.18 (s, 3H), 1.49 (s, 3H), 1.60 (br s, 1H), 2.28 (s, 3H), 2.75-3.00 (m, 5H), 3.50 (d, A part of AB, J = 10.2 Hz, 1H), 3.69 (dd, B part of AB, J = 10.2 and 1.0 Hz, 1H), 7.05-7.20 (m, 4H), 7.61 (s, 1H), 8.59 (s, 1H), 9.97 (s, 1H).
MS (EI) m/z; 433$[M]^+$ (bp).

Synthesis example 32

Yield: 82 %
Orange solid
^{1}H-NMR ($CDCl_3$) δ : 1.18 (s, 3H), 1.48 (s, 3H), 2.27 (s, 3H), 2.80-3.00 (m, 6H), 3.49 (d, A part of AB, J = 10.1 Hz, 1H), 3.69 (dd, B part of AB, J = 10.1 and 1.2 Hz, 1H), 7.40-7.50 (m, 4H), 7.62 (s, 1H), 8.63 (s, 1H), 9.99 (s, 1H).
MS (EI) m/z; 467 $[M]^+$, 348 (bp).

Synthesis example 33

Yield: 84 %
Yellow amorphous substance
^{1}H-NMR ($CDCl_3$) δ : 1.19 (s, 3H), 1.49 (s, 3H), 1.58 (br s, 1H), 2.27 (s, 3H), 2.80-2.98 (m, 3H), 3.08-3.23 (m, 2H), 3.50 (d, A part of AB, J= 10.3 Hz, 1H), 3.72 (d, B part of AB, J= 10.3 Hz, 1H), 7.02-7.08 (m, 1H), 7.25-7.28 (m, 2H), 7.61 (s, 1H), 8.68 (s, 1H), 10.00 (s, 1H).
MS (EI) m/z; 467 $[M]^+$, 354 (bp).

Synthesis example 34

Yellow crystal
mp. : 160.0-165.0 °C
^{1}H-NMR ($CDCl_3$) δ : 1.33 (s, 3H), 1.53 (s, 3H), 2.14 (s, 3H), 2.61 (d,

J = 2.8 Hz, 1H), 3.79 (dd, J = 2.8, 8.8 Hz, 1H), 3.99 (d, J = 8.8 Hz, 1H), 6.78 (d, J = 8.0 Hz, 2H), 6.83 (t, J = 7.6 Hz, 1H), 7.23 (t, J = 8.0 Hz, 2H), 7.66 (s, 1H), 8.59 (s, 1H), 9.79 (s, 1H).
MS (EI) m/z; 371[M]$^+$, 299, 257 (bp).

Synthesis example 35

Yield: 87 %

Yellow amorphous substance, 1:1 mixture of Diastereoisomers.
^{1}H-NMR ($CDCl_3$) δ : 1.15 (s, 6H), 1.29 (d, J = 5.5 Hz, 6H), 1.45 (s, 3H), 1.48 (s, 3 H), 2.28 (s, 3H), 2.29 (s, 3H), 2.58 (br s, 1H), 2.75-2.90 (m, 8H), 2.95 (br s, 1H), 3.37 (d, J = 10.0 Hz, 1H), 3.50 (d, J = 10.0 Hz, 1H), 3.62 (d, J = 10.1 Hz, 1H), 3.64 (d, J = 10.1 Hz, 1H), 7.20-7.38 (m, 10H), 7.59 (s, 1H), 7.60 (s, 1H), 8.45 (s, 1H), 8.65 (s, 1H), 9.95 (s, 1H), 10.00 (s, 1H).
MS (EI) m/z; 414[M+1]$^+$, 279 (bp).

Synthesis example 36

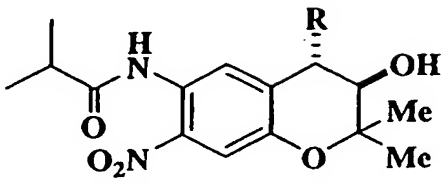
Yield: 27 %

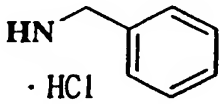
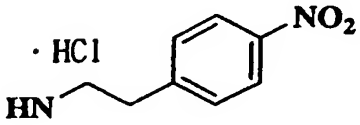
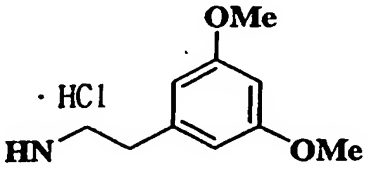
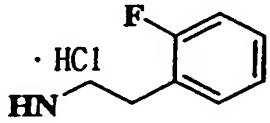
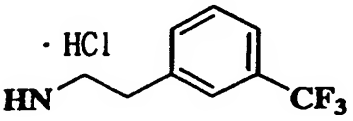
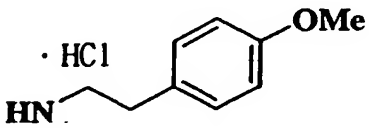
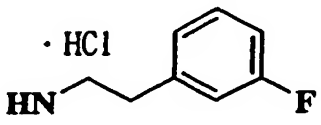
Orange solid, Diastereoisomer A (more polar) .
^{1}H-NMR ($CDCl_3$) δ : 1.20 (s, 3H), 1.29 (d, J = 6.5 Hz, 3H), 1.44 (s, 3H), 1.72 (br s, 2H), 2.26 (s, 3H), 2.61 (dd, A part of AB, J = 13.4 and 7.1 Hz, 1H), 2.86 (dd, B part of AB, J = 13.4 and 6.5 Hz, 1H), 3.28-3.36 (m, 1H), 3.34 (d, A part of AB, J = 9.7 Hz, 1H), 3.63 (dd, B part of AB, J = 9.7 and 1.1 Hz, 1H), 7.14 (d, J = 8.2 Hz, 2H), 7.26 (d, J = 8.2 Hz, 2H), 7.60 (s, 1H), 8.84 (s, 1H), 10.06 (s, 1H).
MS (EI) m/z; 447 [M]$^+$ (bp).

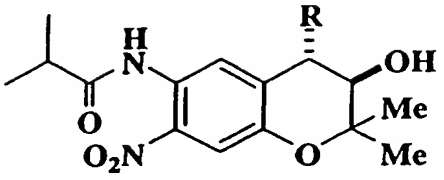
Yield: 32 %

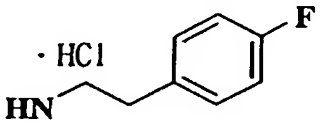
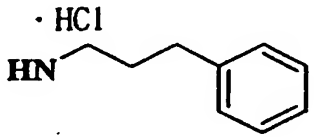
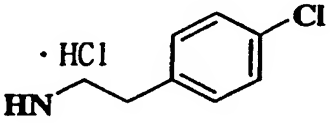
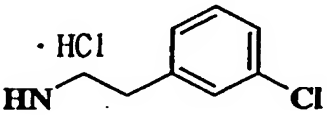
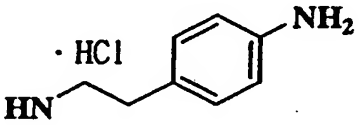
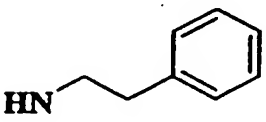
Yellow solid, Diastereoisomer B (less polar).
^{1}H-NMR ($CDCl_3$) δ : 1.14 (d, J = 6.0 Hz, 3H), 1.23 (s, 3H), 1.49 (s, 3H), 1.60 (br s, 2H), 2.29 (s, 3H), 2.76 (d, J = 6.8 Hz, 2H), 3.52 (d, A part of AB, J = 10.0 Hz, 1H), 3.51 (dq, J = 6.8 and 6.0 Hz, 1H), 3.65 (dd, B part of AB, J = 10.0 and 1.0 Hz, 1H), 7.25 (s, 4H), 7.56 (s, 1H), 8.54 (s, 1H), 9.91 (s, 1H).
MS (EI) m/z; 447 [M]$^+$ (bp).

Synthesis examples 37-49



Synthesis example No.	R
37	
38	
39	
40	
41	
42	
43	



Synthesis example No.	R
44	
45	
46	
47	
48	
49	

General procedure for synthesis of compounds 37-49

To a solution of 6-isopropylamido-3,4-epoxy-3,4-dihydro-2,2-dimethyl-7-nitro-2H-1-benzopyran (200 mg, 0.65 mmol) and lithium bromide (226 mg, 2.6 mmol) in tetrahydrofuran (2 mL), amine (1.31 mmol) was added at the room temperature and stirred at 65°C

for 4 hours. Thereto, ethyl acetate was added, and the formed organic phase was washed twice with an aqueous saturated sodium chloride solution and dried over anhydrous magnesium sulfate. After the solvent was distilled off, the residue was purified by silica gel column chromatography, to obtain the intended substance as the crude product. Subsequently, to a solution of the intended substance in methanol (10 times by volume), a 10% hydrogen chloride - methanol solution (twice by volume) was added with ice-cooling and stirred for 30 minutes. Thereto, diisopropylether (100 timed by volume) was added, and the obtained crystals were filtered off, washed with diisopropylether, to obtain the intended hydrochloride. After the obtained hydrochloride was extracted with ethyl acetate and an aqueous saturated sodium hydrogencarbonate solution, ^{1}H-NMR was determined.

Synthesis example 37

Yield: 33 %

Yellow crystal

mp. : 228 °C (decomp.).

MS (FAB) m/z; 414[M+H]$^+$.

Synthesis example 38

Yield: 30 %

Yellow crystal

mp. : 257 °C (decomp.).

^{1}H-NMR ($CDCl_3$) δ : 1.18 (s, 3H), 1.32 (d, J = 6.8 Hz, 6 H), 1.49 (s, 3H), 1.60 (br s, 1H), 2.65 (quint, J = 6.8 Hz, 1H), 2.80 (br s, 1H), 2.95-3.05 (m, 4H), 3.50 (d, A part of AB, J = 10.3 Hz, 1H), 3.68 (d, B part of AB, J = 10.3 Hz, 1H), 7.44 (d, J = 8.4 Hz, 2H), 7.64 (s, 1H), 8.17 (d, J = 8.4 Hz, 2H), 8.74 (s, 1H), 10.18 (s, 1H).

MS (FAB) m/z; 473 [M+H]$^+$.

Synthesis example 39

Yield: 33 %

Yellow crystal

mp. : 244-245 °C (decomp.).
^{1}H-NMR ($CDCl_3$) δ : 1.18 (s, 3H), 1.30 (d, J = 6.8 Hz, 6H), 1.48 (s, 3H), 1.60 (br s,1H), 2.63 (quint, J = 6.8 Hz, 1H), 2.77 (t, J = 6.8 Hz, 2H), 2.95-3.00 (m, 3H), 3.50 (d, A part of AB, J = 10.3 Hz, 1H), 3.68 (d, B part of AB, J = 10.3 Hz, 1H), 3.78 (s, 6H), 6.32 (d, J = 2.4 Hz, 1H), 6.40 (d, J = 2.4 Hz, 2H), 7.62 (s, 1H), 8.71 (s, 1H), 10.14 (s, 1H).
MS (FAB) m/z; 488 $[M+H]^+$.

Synthesis example 40
Yield: 46 %
Yellow crystal
mp. : 239 °C (decomp.).
MS (FAB) m/z; 446 $[M+H]^+$.

Synthesis example 41
Yield: 38 %
Yellow crystal
mp. : 249 °C (decomp.).
MS (FAB) m/z; 496 $[M+H]^+$.

Synthesis example 42
Yield: 23 %
Yellow crystal
mp. : 228 °C (decomp.).
MS (FAB) m/z; 458 $[M+H]^+$.

Synthesis example 43
Yield: 31 %
Yellow crystal
mp. : 243 °C (decomp.).
MS (FAB) m/z; 446 $[M+H]^+$.

Synthesis example 44
Yield: 26 %
Yellow crystal

mp. : 242 °C (decomp.).
^{1}H-NMR ($CDCl_3$) δ : 1.17 (s, 3H), 1.31 (d, J = 6.9 Hz, 6H), 1.48 (s, 3H), 2.00 (br s, 2H), 2.64 (quint, J = 6.9Hz, 1H), 2.75-3.00 (m, 4H), 3.50 (d, A part of AB, J = 10.0 Hz, 1H), 3.69 (d, B part of AB, J = 10.0 Hz, 1H), 7.01 (t, J = 8.5 Hz, 2H), 7.15-7.26 (m, 2H), 7.63 (s, 1H), 8.69 (s, 1H), 10.15 (s, 1H).
MS (FAB) m/z; 446 $[M+H]^+$.

Synthesis example 45
Yield: 9 %
Yellow crystal
mp. : 112-116 °C (decomp.).
MS (FAB) m/z; 442 $[M+H]^+$.

Synthesis example 46
Yield: 24 %
Yellow crystal
mp. : 250 °C (decomp.).
^{1}H-NMR ($CDCl_3$) δ : 1.18 (s, 3H), 1.32 (d, J = 7.0 Hz, 6H), 1.49 (s, 3H), 1.62 (br s, 2H), 2.65 (quint, J = 7.0 Hz, 1H), 2.81 (t, J = 6.6 Hz, 2H), 2.88-3.00 (m, 2H), 3.48 (d, A part of AB, J = 10.3 Hz, 1H), 3.66 (d, B part of AB, J = 10.3 Hz, 1H), 7.18 (d, J = 8.3 Hz, 2H), 7.26 (d, J = 8.3 Hz, 2H), 7.63 (s, 1H), 8.71 (s, 1H), 10.16 (s, 1H).
MS (FAB) m/z; 462 $[M+H]^+$.

Synthesis example 47
Yield: 35 %
Yellow crystal
mp. : 249 °C (decomp.).
MS (FAB) m/z; 462 $[M+H]^+$.

Synthesis example 48
Yield: 16 %
Yellow crystal
mp. : 204-208 °C (decomp.).

MS (FAB) m/z; 443 $[M+H]^+$.

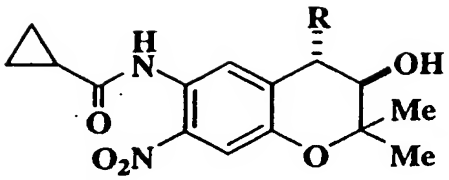
Synthesis example 49

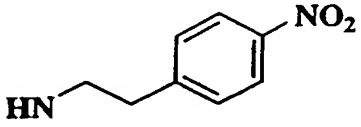
Red amorphous substance

^{1}H-NMR ($CDCl_3$) δ : 1.17 (s, 3H), 1.32 (d, J = 7.0 Hz, 6H), 1.48 (s, 3H), 2.27 (s, 3H), 2.65 (q, J = 7.0 Hz, 1H), 2.86-2.98 (m, 4H), 3.46 (d, J = 10.0 Hz, 1H), 3.68 (d, J = 10.0 Hz, 1H), 7.22-7.32 (m, 5H), 7.61 (s, 1H), 8.63 (s, 1H), 9.98 (s, 1H).

MS (EI) m/z; 420$[M+1]^+$, 344, 179 (bp).

Synthesis examples 50-75



Synthesis example No.	R
5 0	
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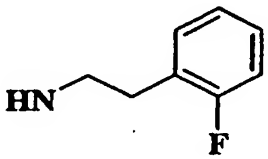
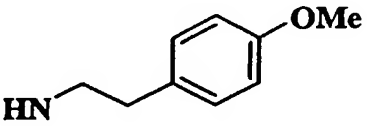
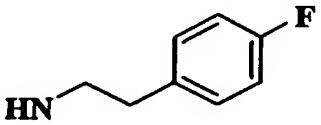
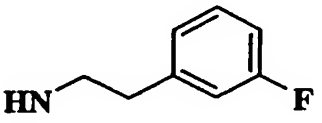
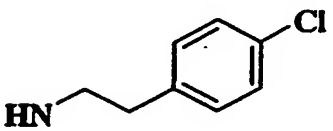
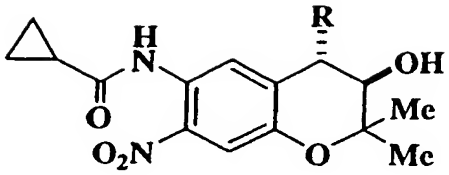
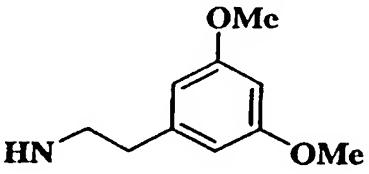
5 2	
5 3	
5 4	
5 5	
5 6	



Synthesis example No.	R
57	
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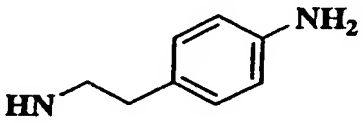
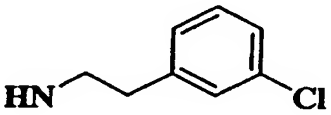
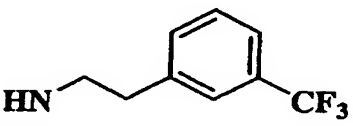
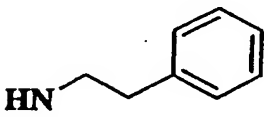
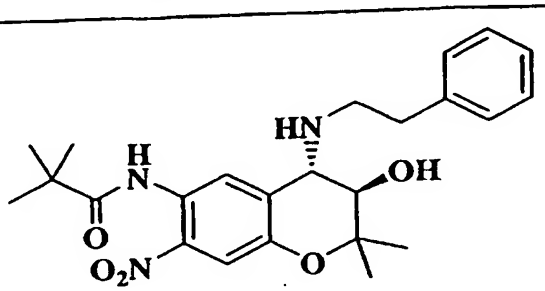
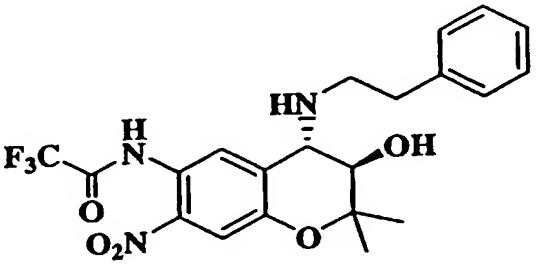
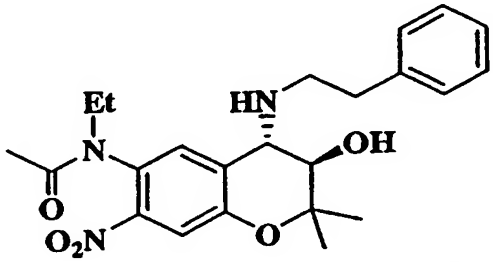
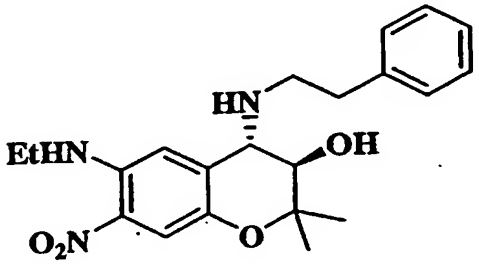
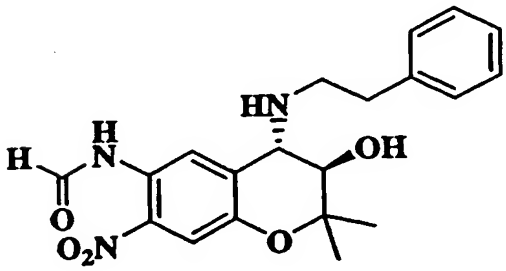
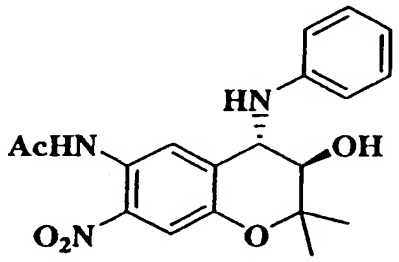
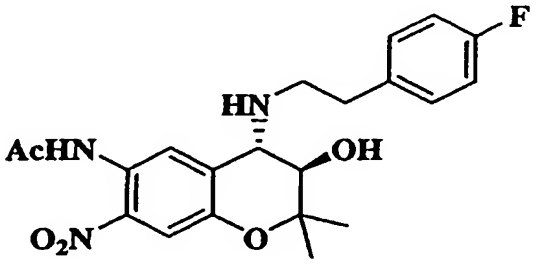
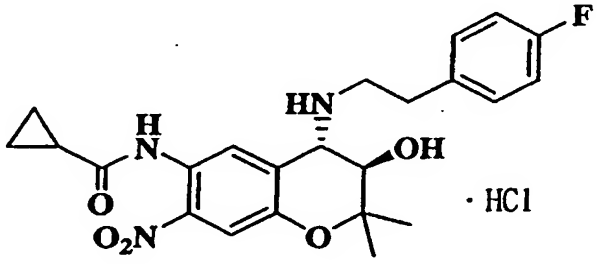
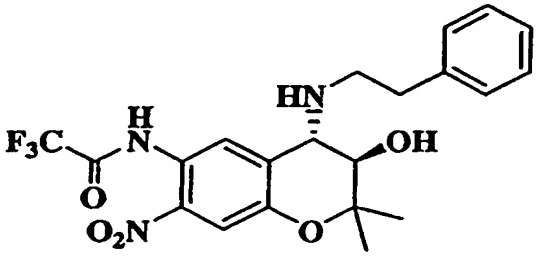
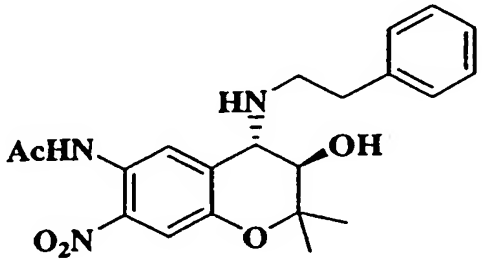
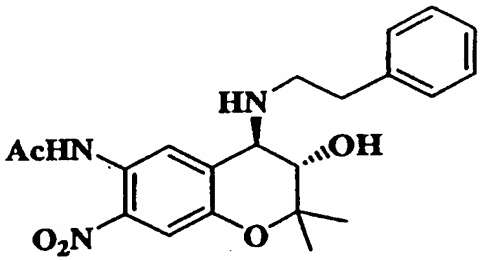
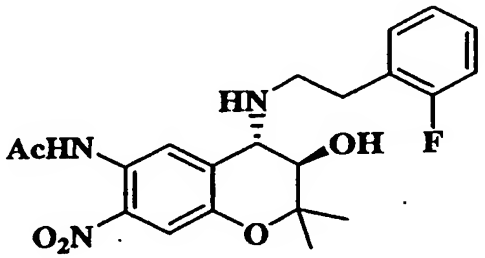
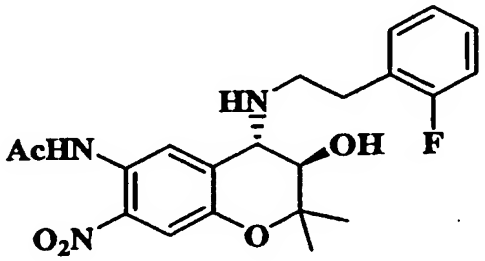
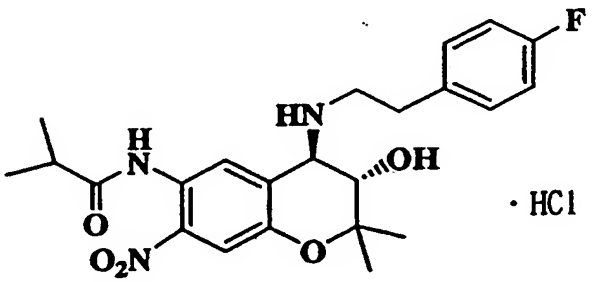
59	
60	
61	
62	

Synthesis example No.	Structural formula
6 3	
6 4	
6 5	
6 6	
6 7	

Synthesis example No.	Structural formula
6 8 (optically active)	
6 9 (optically active)	
7 0 (optically active)	
7 1 (optically active)	

Synthesis example No.	Structural formula
7 2 (optically active)	
7 3 (optically active)	
7 4 (optically active)	
7 5 (optically active)	
7 6 (optically active)	

General procedure for synthesis of compounds 50-75

To a solution of 6-cyclopropylamido-3,4-epoxy-3,4-dihydro-2,2-dimethyl-7-nitro-2H-1-benzopyran (200 mg, 0.66 mmol) and lithium bromide (226 mg, 2.6 mmol) in tetrahydrofuran (2 mL), amine (1.31 mmol) was added at the room temperature and stirred at 65°C for 4 hours. Thereto, ethyl acetate was added, and the formed organic phase was washed twice with an aqueous saturated sodium chloride solution, and dried over anhydrous magnesium sulfate. After the solvent was distilled off, the residue was purified by silica gel column chromatography, to obtain the intended substance.

Synthesis example 50

Yield: 30 %

^{1}H-NMR ($CDCl_3$) δ : 0.96-0.98 (m, 2H), 1.10-1.78 (m, 5H), 1.48 (s, 3H), 1.63-1.66 (m, 1H), 2.93-3.01 (m, 4H), 3.52 (d, J =10.1 Hz, 1H), 6.68 (d, J =10.1 Hz, 1H), 7.40-7.42 (m, 2H), 7.63 (s, 1H), 8.14-8.17 (m, 2H), 8.66 (s, 1H), 10.29 (bs, 1H).

MS (EI) m/z; 334 (bp), 471 $[M]^+$.

Synthesis example 51

Yield: 38 %

^{1}H-NMR ($CDCl_3$) δ : 0.92-0.95 (m, 2H), 1.09-1.13 (m, 2H), 1.19 (s, 3H), 1.50 (s, 3H), 1.63-1.64 (m, 1H), 1.80-1.84 (m, 2H), 2.58-2.68 (m, 4H), 3.56 (d, J =10.1 Hz, 1H), 3.71 (dd, J =0.9, 10.1 Hz, 1H), 7.14-7.27 (m, 5H), 7.61 (s, 1H), 8.72 (d, J =0.9 Hz, 1H), 10.30 (bs, 1H).

MS (EI) m/z; 300 (bp), 439 $[M]^+$.

Synthesis example 52

Yield: 71 %

^{1}H-NMR ($CDCl_3$) δ : 0.94-0.96 (m, 2H), 1.10-1.17 (m, 5H), 1.47 (s, 3H), 1.63-1.66 (m, 1H), 2.81-2.94 (m, 4H), 3.50 (d, J =10.1 Hz, 1H), 3.70 (d, J =10.1 Hz, 1H), 6.96-7.22 (m, 4H), 7.60 (s, 1H), 8.64 (s, 1H), 10.25 (bs, 1H).

MS (EI) m/z; 303 (bp), 443 $[M]^+$.

Synthesis example 53

Yield: 47 %

^{1}H-NMR ($CDCl_3$) δ : 0.93-0.96 (m, 2H), 1.10-1.17 (m, 5H), 1.48 (s, 3H), 1.63-1.65 (m, 1H), 2.72-2.89 (m, 4H), 3.50 (d, J =10.1 Hz, 1H), 3.67 (dd, J =0.7, 10.1 Hz, 1H), 3.77 (s, 3H), 6.80-6.82 (m, 2H), 7.10-7.13 (m, 2H), 7.60 (s, 1H), 8.63 (s, 1H), 10.25 (bs, 1H).

MS (FAB) m/z; 121, 456 $[M+1]^+$.

Synthesis example 54

Yield: 54 %

^{1}H-NMR ($CDCl_3$) δ : 0.95-0.97 (m, 2H), 1.10-1.17 (m, 2H), 1.26 (s, 3H), 1.48 (s, 3H), 1.63-1.67 (m, 1H), 2.76-2.94 (m, 4H), 3.50 (d, J=10.2 Hz, 1H), 3.67 (dd, J=1.0, 10.2 Hz, 1H), 6.94-6.99 (m, 2H), 7.15-7.26 (m, 2H), 7.61 (s, 1H), 8.61 (d, J =1.0 Hz, 1H), 10.26 (bs, 1H).

MS (EI) m/z; 260 (bp), 443 $[M]^+$.

Synthesis example 55

Yield: 53 %

^{1}H-NMR ($CDCl_3$) δ : 0.94-0.97 (m, 2H), 1.11-1.17 (m, 5H), 1.48 (s, 3H), 1.63-1.65 (m, 1H), 2.79-2.94 (m, 4H), 3.49 (d, J =10.3 Hz, 1H), 3.67 (dd, J =0.9, 10.3 Hz, 1H), 6.90-7.01 (m, 3H), 7.23-7.26 (m, 1H), 7.62 (s, 1H), 8.63 (d, J =0.9 Hz, 1H), 10.27 (bs, 1H).

MS (EI) m/z; 301 (bp), 443 $[M]^+$.

Synthesis example 56

Yield: 58 %

^{1}H-NMR ($CDCl_3$) δ : 0.87-0.90 (m, 2H), 1.11-1.14 (m, 2H), 1.17 (s, 3H), 1.48 (s, 3H), 1.63-1.67 (m, 1H), 2.77-2.81 (m, 2H), 2.89-2.93 (m, 2H), 3.48 (d, J =10.3 Hz, 1H), 3.65 (d, J =10.3 Hz, 1H), 7.16-7.26 (m, 4H), 7.62 (s, 1H), 8.65 (s, 1H), 10.28 (bs, 1H).

MS (EI) m/z; 305 (bp), 460 $[M]^+$.

Synthesis example 57

Yield: 56 %

^{1}H-NMR ($CDCl_3$) δ : 0.92-0.95 (m, 2H), 1.09-1.18 (m, 5H), 1.49 (s, 3H), 1.62-1.65 (m, 1H), 2.73-2.92 (m, 4H), 3.51 (d, J=10.2Hz, 1H), 3.67

(d, J =10.2 Hz, 1H), 3.77 (s, 6H), 6.31 (s, 3H), 6.37 (s, 2H), 7.61 (s, 1H), 8.64 (s, 1H), 10.26 (bs, 1H).
MS (EI) m/z; 470 (bp), 486 $[M]^+$.

Synthesis example 58
Yield: 52 %
^{1}H-NMR ($CDCl_3$) δ : 0.92-0.97 (m, 2H), 1.10-1.16 (m, 2H), 1.20 (s, 3H), 1.51 (s, 3H), 1.63-1.68 (m, 1H), 3.64 (d, J =10.1 Hz, 1H), 3.77-3.84 (m, 3H), 7.25-7.39 (m, 5H), 7.67 (s, 1H), 8.88 (s, 1H), 10.34 (bs, 1H).
MS (EI) m/z; 339 (bp), 411 $[M]^+$.

Synthesis example 59
Yield: 57 %
^{1}H-NMR ($CDCl_3$) δ : 0.93-0.96 (m, 2H), 1.11-1.17 (m, 5H), 1.47 (s, 3H), 1.63-1.65 (m, 1H), 2.68-2.71 (m, 2H), 2.85-2.88 (m, 2H), 3.46 (d, J =10.1 Hz, 1H), 3.64 (d, J =10.1 Hz, 1H), 6.62-6.64 (m, 2H), 6.70-7.02 (m, 2H), 7.61 (s, 1H), 8.64 (s, 1H), 10.26 (bs, 1H).
MS (EI) m/z; 333 (bp), 439 $[M]^+$.

Synthesis example 60
Yield: 42 %
^{1}H-NMR ($CDCl_3$) δ : 0.94-0.97 (m, 2H), 1.12-1.17 (m, 5H), 1.49 (s, 3H), 1.63-1.67 (m, 1H), 2.77-2.94 (m, 4H), 3.49 (d, J =10.3 Hz, 1H), 3.67 (dd, J =0.9, 10.3 Hz, 1H), 7.10-7.22 (m, 4H), 7.62 (s, 1H), 8.63 (d, J =0.9 Hz, 1H), 10.27 (bs, 1H).
MS (EI) m/z; 334 (bp), 460 $[M]^+$.

Synthesis example 61
Yield: 61 %
^{1}H-NMR ($CDCl_3$) δ : 0.94-0.97 (m, 2H), 1.10-1.18 (m, 5H), 1.48 (s, 3H), 1.63-1.66 (m, 1H), 2.85-2.96 (m, 4H), 3.53 (d, J =10.1 Hz, 1H), 3.71 (d, J =10.1 Hz, 1H), 7.28-7.46 (m, 4H), 7.60 (s, 1H), 8.66 (s, 1H), 10.26 (bs, 1H).
MS (EI) m/z; 259 (bp), 494 $[M]^+$.

Synthesis example 62

Red amorphous substance

^{1}H-NMR ($CDCl_3$) δ : 0.94-0.97 (m, 2H), 1.12-1.15 (m, 2H), 1.16 (s, 3H), 1.47 (s, 3H), 1.61-1.67 (m, 1H), 2.79-2.96 (m, 4H), 3.45 (d, J = 9.9 Hz, 1H), 3.64 (d, J = 9.9 Hz, 1H), 7.22-7.32 (m, 5H), 7.61 (s, 1H), 8.62 (s, 1H), 10.26 (s, 1H)

MS (EI) m/z; 418[M+1]$^+$, 346, 309, 179 (bp).

Synthesis example 63

Red crystal

mp. : 169.0-170.0 °C

^{1}H-NMR ($CDCl_3$) δ : 1.17 (s, 3H), 1.37 (s, 9H), 1.47 (s, 3H), 2.81-2.85 (m, 2H), 2.93-2.97 (m, 2H), 3.47 (d, J = 10.1 Hz, 1H), 3.67 (d, J = 10.1 Hz, 1H), 7.19-7.32 (m, 5H), 7.63 (s, 1H), 8.74 (s, 1H), 10.44 (s, 1H).

MS (EI) m/z; 441[M+1]$^+$, 322, 268 (bp).

Synthesis example 64

Red crystal

mp. : 176.5-178.0 °C

^{1}H-NMR ($CDCl_3$) δ : 1.18 (s, 3H), 1.54 (s, 3H), 3.05-3.16 (m, 3H), 3.26-3.30 (m, 1H), 4.06 (d, J = 8.6 Hz, 1H), 4.58 (d, J = 8.6 Hz, 1H), 7.15-7.26 (m, 5H), 7.73 (s, 1H), 8.65 (s, 1H), 10.66 (s, 1H).

MS (EI) m/z; 453[M]$^+$ (bp).

Synthesis example 65

Red amorphous substance

^{1}H-NMR ($CDCl_3$) δ : 1.02 (t, J = 6.8 Hz, 3H), 1.24 (s, 3H), 1.52 (s, 3H), 1.83 (s, 3H), 2.68-2.96 (m, 4H), 3.33 (q, J = 6.8 Hz, 1H), 3.63 (d, J = 10.1 Hz, 1H), 3.74 (d, J = 10.1 Hz, 1H), 3.77-3.90 (m, 1H), 7.19-7.39 (m, 7H).

MS (FAB) m/z; 428[M]$^+$ (bp), 268, 105.

Synthesis example 66

Red amorphous substance

^{1}H-NMR ($CDCl_3$) δ : 1.15 (s, 3H), 1.33 (t, J = 7.1 Hz, 3H), 1.46 (s,

3H), 2.82-2.86 (m, 3H), 2.91-2.96 (m, 1H), 3.08-3.13 (m, 2H), 3.59 (d, J=10.1 Hz, 1H), 3.65 (d, J=10.1 Hz, 1H), 6.58 (s, 1H), 7.22-7.26 (m, 3H), 7.31-7.34 (m, 2H), 7.53 (brs, 1H), 7.60 (s, 1H),
MS (EI) m/z; 385$[M]^+$, 314, 266, 223 (bp).

Synthesis example 67

Yellow oil
^{1}H-NMR ($CDCl_3$) δ : 1.18 (s, 3H), 1.48 (s, 3H), 2.75-3.00 (m, 6H), 3.52 (d, A part of AB, J = 9.9 Hz, 1H), 3.70 (d, B part of AB, J = 9.9 Hz, 1H), 7.18-7.35 (m, 5H), 7.62 (s, 1H), 8.45 (s, 1H), 8.66 (s, 1H), 9.98 (s, 1H).
MS (EI) m/z; 385$[M]^+$, 313 (bp).

Synthesis example 68

Derived from (+)-(3*R**, 4*R**)-6-acetamide-3,4-epoxy-3,4-dihydro-2,2-dimethyl-7-nitro-2H-1-benzopyran (99% ee or more).
Yellow amorphous substance
$[\alpha]_D^{26}$ +104.6 (*c* 0.64, EtOH)

Synthesis example 69

Derived from (+)-(3*R**, 4*R**)-6-acetamide-3,4-epoxy-3,4-dihydro-2,2-dimethyl-7-nitro-2H-1-benzopyran (99% ee or more).
Yellow crystal
(HCl salt): mp. 246-247 °C (decomp.).
(HCl salt): $[\alpha]_D^{26}$ -71.8 (*c* 0.38, EtOH)

Synthesis example 70

Derived from (+)-(3*R**, 4*R**)-3,4-epoxy-6-cyclopropylamide-3,4-dihydro-2,2-dimethyl-7-nitro-2H-1-benzopyran (99% ee or more).
(HCl salt): Yellow crystal
(HCl salt): mp. 241-246 °C (decomp.).
(HCl salt): $[\alpha]_D^{26}$ -92.1 (*c* 0.45, EtOH)

Synthesis example 71

Derived from (+)-(3*R**, 4*R**)-3,4-epoxy-3,4-dihydro-2,2-

dimethyl-7-nitro-6-trifluoroacetamide-2H-1-benzopyran (99% ee or more).

(HCl salt): Yellow crystal

(HCl salt): mp. 243 °C (decomp.).

$[\alpha]^{26}_{D}$ -54.8 (*c* 0.5, EtOH)

Synthesis example 72

Derived from (+)-(3R*, 4R*)-6-acetamide-3,4-epoxy-3,4-dihydro-2,2-dimethyl-7-nitro-2H-1-benzopyran (99% ee or more).

Red amorphous substance

$[\alpha]^{26}_{D}$ -64.3 (*c* 1.03, EtOH)

Synthesis example 73

Derived from (-)-(3R*, 4R*)-6-acetamide-3,4-epoxy-3,4-dihydro-2,2-dimethyl-7-nitro-2H-1-benzopyran (99% ee or more).

Red amorphous substance

$[\alpha]^{26}_{D}$ +61.2 (*c* 0.98, EtOH)

Synthesis example 74

Derived from (+)-(3R* , 4R*)-6-acetamide-3,4-epoxy-3,4-dihydro-2,2-dimethyl-7-nitro-2H-1-benzopyran (99% ee or more).

Red amorphous substance

$[\alpha]^{26}_{D}$ -64.6 (*c* 1.00, EtOH)

Synthesis example 75

Derived from (-)-(3R*, 4R*)-6-acetamide-3,4-epoxy-3,4-dihydro-2,2-dimethyl-7-nitro-2H-1-benzopyran (99% ee or more).

Red amorphous substance

$[\alpha]^{26}_{D}$ +60.8 (*c* 0.93, EtOH)

Synthesis example 76

To a solution of (+)-(3R*, 4R*)-3,4-epoxy-6-isopropylamide-3,4-dihydro-2,2-dimethyl-7-nitro-2H-1-benzopyran (1.0 g, 3.59 mmol) and lithium bromide (1.24 g, 14.36 mmol) in acetonitrile (10 mL), 4-fluorophenethylamine (1.88mL, 14.4 mmol) corresponding to respective 4-position substituent was added at

the room temperature and stirred at 65°C for 2 hours. Thereto, ethyl acetate was added, and the formed organic phase was washed with a saturated sodium hydrogencarbonate solution and an aqueous saturated sodium chloride solution and dried over anhydrous magnesium sulfate. After the solvent was distilled off, the residue was purified by silica gel column chromatography, to obtain the substance substituted by amine at 4-position. Subsequently, to a solution of the substance substituted by amine at 4-position in ethanol (10 times by volume), concentrated hydrochloric acid (6 equivalents) was added at the room temperature and heated to reflux at 90°C for 1 day. Thereto, a saturated sodium hydrogencarbonate solution was added and extracted with ethyl acetate, and the formed organic phase was washed once with an aqueous saturated sodium chloride solution and dried over anhydrous magnesium sulfate. The solvent was distilled off, to obtain the substance deamidated at 6-position. Subsequently, to a solution of the substance deamidated at 6-position in dimethylformamide (20 times by volume), a 4N hydrogen chloride - dioxane solution (1.4 equivalents) was added at the room temperature and stirred for 10 minutes. An acid chloride (1.5 equivalents) corresponding to the 6-position substituent was added dropwise and stirred for 1 hour, then methanol (1 mL) was added and stirred further for 10 minutes. Thereto, water was added and extracted with ethyl acetate, and the formed organic phase was washed with a saturated sodium hydrogencarbonate solution and an aqueous saturated sodium chloride solution and dried over anhydrous magnesium sulfate. After the solvent was distilled off, the residue was purified by silica gel column chromatography, to obtain the intended substance. Subsequently, to a solution of the intended substance in methanol (10 times by volume), a 10% hydrogen chloride - methanol solution (twice by volume) was added with ice-cooling and stirred for 30 minutes. Thereto, diisopropylether (100 times by volume) was added, and the obtained crystals were filtered off, washed with diisopropylether, to obtain the intended hydrochloride.

Yellow crystal
mp. : 244-245 °C (decomp.).

$[\alpha]^{26}_{D}$ -67.3 (c 0.4, EtOH)

[Preparation Examples]

Preparation Example 1

Tablet:

a compound according to the invention	10 g
lactose	260 g
crystal cellulose powder	600 g
corn starch	350 g
hydroxypropyl cellulose	100 g
CMC-Ca	150 g
magnesium stearate	30 g
total	1,500 g

The above-mentioned compounds were mixed by a usual method and thereafter 10,000 sugar-coated tablets each containing 1 mg of the active ingredient per a tablet were prepared.

Preparation Example 2

Capsule:

a compound according to the invention	10 g
lactose	440 g
crystal cellulose powder	1,000 g
magnesium stearate	50 g
total	1,500 g

The above-mentioned compounds were mixed by a usual method and thereafter filled in gelatin capsules, to prepare 10,000 capsules each containing 1 mg of the active ingredient per a capsule.

Preparation Example 3

Soft capsule:

a compound according to the invention	10 g
PEG 400	479 g
saturated fatty acid triglyceride	1,500 g
peppermint oil	1 g
Polysorbate 80	10 g
Total	2,000 g

The above-mentioned compounds were mixed by a usual method and thereafter filled in No.3 soft gelatin capsules, to prepare 10,000 soft capsules each containing 1 mg of the active ingredient per a capsule.

Preparation Example 4

Ointment:

a compound according to the invention	1.0 g
liquid paraffin	10.0 g
cetanol	20.0 g
white vaseline	68.4 g
ethylparaben	0.1 g
1-menthol	0.5 g
total	100.0 g

The above-mentioned compounds were mixed by a usual method to obtain 1% ointment.

Preparation Example 5

Suppository:

a compound according to the invention	1 g
Witepsol H15*	478 g
Witepsol H35*	520 g
Polysorbate 80	1 g
Total	1,000 g

(* trade name Witepsol for triglyceride type compounds)

The above-mentioned compounds were melt-mixed by a usual method, poured into suppository containers and cooled to solidify, thereby 1,000 suppositories (1 g) each containing 1 mg of the active

ingredient per a suppository were prepared.

Preparation Example 6

Injection:

a compound according to the invention	1 mg
distilled water for injection	5 mL

It is used by dissolving when applied.

[Pharmacological Test Example]

Effects of compound on the functional refractory period in guinea-pig left atrium muscle and right ventricular papillary muscle

Test method

Hearts were removed from guinea-pigs, and left atrium muscle or right ventricular papillary muscle were isolated therefrom in a Krebs-Henseleit solution aerated with 95% O_2 + 5% CO_2. The samples were stimulated electrically at a rate of 1 Hz and a voltage of 1.5 times of the threshold value reacted to stimulation (basic stimulation; S1) by using an electric stimulating apparatus. The contraction occurred at that time was recorded by a thermal stylus recorder via a FD pickup and a strain pressure amplifier. The functional refractory period is defined as the shortest time interval between S1 resulting from determinable contraction and an extra stimulation (S2). The time interval between S1 and S2 in the left atrium muscle sample was started from 150 msec, decreased in 10 msec steps until 100 msec, and thereafter 5 msec steps to the functional refractory period. For the right ventricular papillary muscle sample, it was started from 300 msec and decreased in 10 msec steps until the functional refractory period. Herein, S2 was set at twice of the threshold value which reacted to stimulation. The experimental temperature was 36±1°C. Herein, the solvent did not influence on any of the functional refractory periods for left atrium muscle and right ventricular papillary muscle. After determining the basic value before addition of the compound, the compound was added cumulatively, incubated for 15 minutes for respective concentration, and thereafter the functional

refractory period was determined.

Results

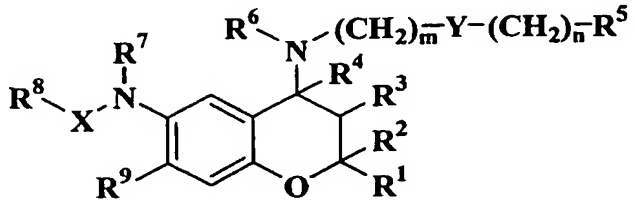
Compounds according to the present invention exhibited strong prolongation effect on the functional refractory period(FRP) on atrium muscle.

Synthesis example No.	Prolongation effect on FRP EC_{20}(μM)	Synthesis example No.	Prolongation effect on FRP EC_{20}(μM)
1	6.1	5	5.5
3	4.0	6	1.4
4	5.0	8	1.8

Compounds according to the present invention exhibit strong prolongation effect on the functional refractory period, thus they are useful for improvement of arrhythmia. Therefore, the present invention can provide useful antiarrhythmic agents.

CLAIMS

1. A benzopyran derivative of the formula (I)



(I)

wherein, R^1 and R^2 represent each independently a hydrogen atom, a C_{1-6} alkyl group in which said alkyl group may be optionally substituted with a halogen atom, a C_{1-6} alkoxy group or a hydroxyl group; or a phenyl group in which said phenyl group may be optionally substituted with a halogen atom, a hydroxyl group, a nitro group, a cyano group, a C_{1-6} alkyl group or a C_{1-6} alkoxy group,

R^3 represents a hydroxyl group or C_{1-6} alkylcarbonyloxy group,

R^4 represents a hydrogen atom, or R^3 and R^4 together form a bond,

m represents an integer of 0-4,

n represents an integer of 0-4,

Y is absent, or represents $CR^{11}R^{12}$ in which R^{11} and R^{12} represent each independently a hydrogen atom or a C_{1-6} alkyl group,

R^5 represents an aryl group or a heteroaryl group in which said aryl group and said heteroaryl group may be optionally substituted with q·(R^{10}), in which R^{10} represents a halogen atom, a hydroxyl group, a C_{1-6} alkyl group in which said alkyl group may be optionally substituted with a halogen atom or a C_{1-6} alkoxy group; or R^{10} represents a nitro group, a cyano group, a formyl group, a formamide group, an amino group, a C_{1-6} alkylamino group, a di-C_{1-6}alkylamino group, a C_{1-6} alkylcarbonylamino group, a C_{1-6} alkylsulfonylamino group, an aminocarbonyl group, a C_{1-6} alkylaminocarbonyl group, a di-C_{1-6} alkylaminocarbonyl group, a C_{1-6} alkylcarbonyl group, a C_{1-6} alkoxycarbonyl group, an aminosulfonyl group, a C_{1-6} alkylsulfonyl group, a carboxyl group or an arylcarbonyl group, q represents an integer of 1-3, and each R^{10} may be same or different if q represents 2 or 3,

R^6 represents a hydrogen atom or a C_{1-6} alkyl group,

R^7 represents a hydrogen atom or a C_{1-6} alkyl group,

X is absent, or represents C=O or SO_2,

R^8 represents a hydrogen atom, a C_{1-6} alkyl group in which said alkyl group may be optionally substituted with a halogen atom, a hydroxyl group or a C_{1-6} alkoxy group; or C_{3-6} cycloalkyl group, and

R^9 represents a hydrogen atom, a halogen atom, a nitro group or a cyano group;

or a pharmaceutically acceptable salt thereof.

2. A benzopyran derivative or pharmaceutically acceptable salt thereof according to claim 1, wherein R^1 and R^2 represent both methyl groups, R^3 represents a hydroxyl group and R^4 represents a hydrogen atom.

3. A benzopyran derivative or pharmaceutically acceptable salt thereof according to claim 2, wherein R^9 represents a hydrogen atom or a nitro group.

4. A benzopyran derivative or pharmaceutically acceptable salt thereof according to claim 3, wherein X represents C=O, and R^6 and R^7 represent both hydrogen atoms.

5. A benzopyran derivative or pharmaceutically acceptable salt thereof according to claim 4, wherein R^5 represents a benzene ring, Y is absent, m represents 0, and n represents 1 or 2.

6. A benzopyran derivative or pharmaceutically acceptable salt thereof according to claim 5, wherein R^8 represents an alkyl group, R^9 represents a nitro group, and n represents 2.

7. A drug characterized by comprising a benzopyran derivative or pharmaceutically acceptable salt thereof according to claim 1 as an active ingredient.

8. A drug for treating arrhythmia characterized by comprising

a benzopyran derivative or pharmaceutically acceptable salt thereof according to claim 1 as an active ingredient.

INTERNATIONAL SEARCH REPORT

Ir ional Application No
PCT/JP 00/06323

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D311/68 C07D405/12 A61K31/453 A61P9/06 C07D311/70

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 91 13865 A (ISIS) 19 September 1991 (1991-09-19) page 18 -page 23; claims; table 2	1-8
A	WO 98 04542 A (NISSAN) 5 February 1998 (1998-02-05) page 148; claims; tables	1-8

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 February 2001	14/02/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Francois, J

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Ir ional Application No
PCT/JP 00/06323

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9113865 A	19-09-1991	EP 0518939 A	23-12-1992
WO 9804542 A	05-02-1998	AU 713573 B	02-12-1999
		AU 3634997 A	20-02-1998
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